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THE INHERITANCE FACTOR IN ENDOCRINE DYSFUNCTION

by

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Illustration

The purpose of this study has been to ascertain the present status of knowledge in regard to the inheritance factor in endocrine dysfunction. The material presented in this thesis, therefore, represents the result of a survey of recent literature in the field of endocrinology with particular emphasis on the material that deals with the genetic implications. No attempt, other than to draw a few conclusions, has been made to evaluate the material or to challenge the authors' statements or the validity of their experiments. The writer has relied on experts in the field for suggestions of source material, on the prestige of authors, and, in the case of magazine articles, on the rating of the professional publications as criteria for evaluating the scientific accuracy of the facts presented. Little use of material published previous to 1920 has been made because of the rapid advances that have been made concurrently in endocrinology and the field of genetics in recent years. More attention has been paid to material published since 1931 since which, Baur states, there has been more or less stabilization in the science of human heredity.

Many difficulties were encountered in a study of this sort, chief of which were, first, the lack of agreement on important points, such as, (a) a standard classification of endocrine disorders, (b) whether certain conditions frequently ascribed to endocrinisms are actually endocrine disturbances, there not having been enough study and experimentation in the case of some of these conditions to warrant a definite conclusion. The second difficulty encountered was the lack of agreement, not only as

to the possible effect of the endocrine glands on inheritance factors, but the way in which such effects, if they exist, may be produced. In some instances it has seemed that authorities have arrived at conclusions on small evidence; in other cases, that environmental factors at times have been confused with hereditary factors. This may be due in part to the fact that some endocrinologists are better students of endocrinology than they are of genetics, and, in part, to the general confusion that exists in regard to the whole subject. In order, therefore, not to misrepresent, authorities have been quoted frequently, often in full.

History, Location and Function of the Endocrine Glands

Although the pituitary has been known since the time of Juvenal and Pliny and ancient literature contains anatomical descriptions of all the endocrine glands except the parathyroids, an understanding of their secretory function was not established until the nineteenth century.

Engelbach (1932a--Vol.1) refers to this early period as the first epoch in the history of endocrinology. It was characterized by the discovery and naming of the glands of the endocrine system. Garrison states that the pituitary was known to Galen, described by Vesalius in 1543, and called the hypophysis by Sömmering in 1778. The thyroid was likewise described by Vesalius in 1543 and named by Wharton in 1656. The thymus was first described by Rufus of Ephesus some two thousand years ago. An account of the suprarenals was given by Eustachius in 1563. They were named the capsula renalis by Spigelius in 1627 and the capsula suprarenals by Riolanus the following year. The parathyroids were first described by Remak in 1855, but credit for their discovery usually goes to Sandström in 1880. He regarded them as merely displaced, undeveloped fragments of thyroid tissue, but a year later their independent functional importance, so Hoskins (1933) states, was discovered by Gley. Engelbach (1932a--Vol.1) credits Kohn in 1899 with being the first to establish their anatomic and physiologic independence.

During the latter part of the fifteenth century, the first theories concerning the functions of the endocrine glands appeared in literature. Garrison, however, points out that the fashionable physician to the

Court of Louis XV, Theopile de Bordeu, was the first to state clearly the function of the internal secretion of the glands. The conception of internal secretion was read into a remark of Bordeu in 1775 to the effect that each organ gives off "emanations" which are necessary for the well being of the parts of the body. Rolleston (1937) suggests that Legallois, the physiologist (1801) was the forerunner of the conception of internal secretion, while Engelbach (1932a--Vol.1) credits Bordeu, Legallois and Bernard with being the originators of the hypothesis of hormonic action.

The first experimental proof of the internal secretion of a gland was made by A. A. Berthold of Göttingen in 1849. Berthold showed that the transplantation of a cock's testes to another part of the body prevented the atrophy of the comb which otherwise follows castration. The same observation in regard to the development of secondary sex characters was made by Knauer and Halbern in 1900 in the case of the ovary.

Berthold's experiment foreshadowed the beginning of the second epoch of endocrine history which was inaugurated by the animal experimentation of Claude Bernard in 1855 to determine the constitutents of glandular secretion. Bernard pointed out that the liver had two important secretions, an external one of bile into the intestines and an internal one of sugar directly into the blood. In the same year, Thomas Addison of Guy's Hospital, London brought out his monograph on "The Constitutional and Local Effects of Diseases of the Supra Renal Capsules." His work stimulated Brown-Séquard, the French physiologist, whose removal of the suprarenals in animals in the following year

confirmed the medical deduction made by Addison. In 1858, Schiff reported the complete excision of the thyroid gland in dogs resulted in death, an effect which is now known to be due to the concomitant accidental removal of the parathyroids.

Following the experimental work of Brown-Séquard and others, there was a rapid accumulation of similar investigations on other endocrine glands. Advances in this period were due to the work of experimental surgeons who produced conditions in animals similar to those found in man. Harvey Cushing was a valuable contributor to this period through his work on the nature and function of the pituitary.

The final result of this progressive experimental period, Engelbach states, was the demonstration that the thyroid, pituitary, parathyroid, gonads, and suprarenal glands have definite effects upon differentiation, development and metabolism of the body and the functions of its other specialized systems. These experiments further demonstrated that these bodily effects were due to the functional interrelationships of the endocrine glands.

While the withdrawal and transplantation experiments of this second period helped to explain some of the complex clinical entities due to endocrine deficiency they were insufficient, Engelbach states, to account for the function of individual glands or their secretory action upon the other organs of the body. These problems were unsolved until the active principles of the glands were isolated. Whereas the experimental surgeon was largely responsible for the progress made during the

second epoch, advancement in the knowledge of endocrinology during the third period was due to the work of the biologist, biochemist, and pharmacologist.

Up to this time, the hypothesis that the endocrine glands exerted a detoxicating effect was widely accepted, and, in the case of the adrenals, was not abandoned until 1894 when Oliver and Schäfer, by experimental injections of extracts of the adrenals, discovered in the adrenal medulla the pressor substance adrenaline. This, the first hormone to be thus established, was isolated simultaneously in 1901 by Takamine and by Aldrich. From 1894 to 1896 the first active principle of the pituitary was independently identified by Oliver and Schäfer, Frankel, Furth and Abel. Following the isolation of thyroxine by Kendall in 1914, the next great advancement was made in 1921 by Evans and Long in the form of the discovery of the growth hormone of the pituitary. Their experiment identified, in addition to the growth hormone, the pituitary sex hormone which has since been confirmed by specific cytologic changes in the Graafian follicle of the ovary by Aschheim and Zondek and by Smith and Engle (1926-1928). About this same time, the active principle of the adrenal cortex, called "cortin" by Hartmann in 1928 and "eschatin" by Swingle and Pfiffner in 1930, has been proved to be the hormone, absence of which is responsible for the symptoms of Addison's Disease. The discovery of the hormone of the adrenal cortex changed the belief that the symptoms of Addison's Disease were due to the absence or deficiency of adrenaline, the active principle of the adrenal medulla.

Pituitary

From the evolutionary standpoint, the pituitary is an ancient organ. It is found in all classes of the vertebrates. In the lowest, it is represented by an open gland in the throat which discharges its secretion directly into the throat. Hoskins (1933) states that there is a suggestion that in the lower forms it may play an even more important part as a regulator than it does in the higher animals.

In the human adult, the hypophysis is situated almost exactly in the center of the head. It is well protected in a saddle shaped recess in the sphenoid bone. The recess is known as the sella turcica. The gland, which consists of an anterior and a posterior lobe, weighs only ten grams or less.

The pituitary, now considered the predominant endocrine gland, was later than the adrenals and the thyroid in attracting modern investigation. Rolleston (1937) states that, in a review of nervous physiology in 1889, it was dismissed as having little if any use in the organism of the higher vertebrates, and in the same year Alexander Macalister, professor of anatomy at Cambridge University, England described it as probably the rudiment of an archaic sense organ.

The existence of the pituitary was known to Galen in 200 A. D. The name pituitary was assigned to it by Vesalius who believed that it collected waste material (Pituita-phelgm or slime) from the brain. The idea of the mucous secreting function was destroyed by Conrad Schneider in the seventeenth century. About the same time Sylvus of Leyden came

to feel that it was concerned in the regulation of the cerebral spinal fluid, an idea that was held as late as 1843 by Magendie.

The condition now known as acromegaly was recognized as a growth anomaly by Vergas in 1864, and an excellent account of it was given by Pierre Marie in 1886. The condition was connected with the pituitary by Minkowski in the following year. Attention was thus directed to the gland, but it was not until this century, especially since 1905, that its physiology and anatomy were exhaustively investigated, particularly by Harvey Cushing whose publication, "The Pituitary Body and Its Disorders" appeared in 1912.

It is now recognized that the pituitary bears much the same relationship to the other endocrine glands that the brain does to the remainder of the body. The hypophysis is now thought to manufacture an increasing number of active principles or hormones, the anterior lobe as many as fourteen and the posterior pituitary seven, although Abel has expressed some doubt as to whether each different action of pituitary extracts is necessarily due to a special hormone. The pituitary hormones act chiefly by stimulating the other endocrine glands, thus the anterior lobe produces the growth hormone, which, aided by the secretions of the thyroid, adrenals and gonads, controls all body growth. The master effect of the pituitary may be summarized as follows: It controls the thyroid and through it regulates the oxidative processes; it controls the liver and through it regulates fat metabolism; it controls the gonads and through them regulates sexual development; it controls the suprarenals

and through them regulates muscular contraction; it controls the kidneys and through them regulates water metabolism; it controls the islands of Langerhans and through them regulates carbohydrate metabolism. In addition, the lactogenic hormone in the female stimulates milk production after the priming of pregnancy and thus aids in the growth of the infant.

Thyroid

The thyroid gland, so called the "pace setter" or metabolic regulator of the body, is located near the upper part of the trachea. It consists of a right and left lobe and an isthmus. Hoskins (1933) has vividly described the location of the thyroid when he says that it straddles the trachea like a well filled pair of panniers thrown over the back of a pack animal. The panniers represent the right and left lobes and the sling represents the isthmus. It is unknown in the invertebrates but is found early in the vertebrate series and becomes more highly developed in the higher animals. In size the normal gland varies within fairly wide limits, averaging usually less than an ounce in weight in the adult.

Historically the thyroid has been known since the time of Juvenal and Pliny. Before the sixteenth century, Roger of Palerno had treated goitre with seaweed iodine. Early scholars regarded the thyroid as a protective device to keep the throat warm; others thought it was established to round out the contour of the neck. The theory that gained most favorable currency in the nineteenth century, Hoskins states, was that the thyroid, like the adrenals and the thymus, had no significance

except during embryonic life. Schiff of Germany was the first to dispute this theory by putting it to test through animal experimentation. He removed the glands from a series of animals following which death ensued. Schiff's observation, however, made no impression on the physiologists largely because of the lack of interest in biological research at that time.

In 1836 William King, lecturer in pathology at Guy's Hospital, London, described the passage of secretion of the thyroid into the lymphatics and so into the great veins. He thus anticipated the concept of the thyroid as a gland of internal secretion. Between 1835 and 1840 Graves and Basedow described exophthalmic goitre and in 1871 the association of thyroid disorder with mental deficiency was established.

The knowledge that the symptoms of endocrine inadequacy were due to the absence or diminution of an internal secretion present in and necessary for health was first established in the case of the thyroid. It was recognized that natural absence of the thyroid gland in adults causes the disease myxoedema; in children, it results in arrested growth; and in children and adults, complete removal of the glands is soon followed by thyroid deficiency. For this knowledge science is indebted to clinicians rather than to physiologists. In 1871 Hilton Fagge described sporadic cretinism and prophesized that it might occur in adult life. Two years later, surgeon Sir William Gull reported the cases of five women who presented a typical picture of what is now known as myxoedema. Four years later another British physician,

W. M. Ord, performed a post mortem examination on one of his patients who was afflicted with a condition similar to that found in Gull's patients, and, because of the mucilaginous material in the tissues which he found under the skin, called the new disease, myxoedema. This was followed by active research in the thyroid. Surgeons began to treat goitre by radical operation. Rederdin of Geneva reported a few of these in 1833 and the same year Kosher of Bern gave an extensive report that included a discussion of the after effects of complete removal of a goitrous gland. He stressed particularly the marked interference with nutrition. Semon, the same year, called attention to the similarity between the symptoms of myxoedema and those following the removal of the thyroid. He suggested that the gland might be of fundamental importance to life. The findings of these workers stimulated Schiff who repeated and extended his earlier experiments with dogs. He found that complete removal of the gland was commonly followed by death and that the symptoms in various respects closely resembled those that followed the complete removal of goitrous glands in man.

The recognition of the influence of the thyroid on mental development led to experimentation in substitution therapy in cases of deficiency. The injection of an emulsion of the gland was first administered by G. R. Murray in 1891. The isolation of thyroxine by Kendall of the Mayo Clinic in 1914 has provided a specific for thyroid deficiency which has made it possible to supply artificially a sufficient amount of the missing hormone.

Studies to determine the effects of overactivity of the thyroid have failed to prove that, whereas underproduction of thyroxine results in a characteristic sluggishness of mind and retarded physical development, overproduction results in brilliance of mind. Too much thyroid secretion seems to disturb the rhythm of growth; it overstimulates the nervous system, increases the metabolic rate and thus makes its victims nervously and emotionally unstable. According to our present knowledge, therefore, the function of the thyroid is to control metabolism and in cooperation with the pituitary to exert an indispensable influence on physical growth and development. The thyreotropic hormone is sent out by the pituitary to stimulate the thyroid gland to exert its influence on growth.

Parathyroids

The parathyroids are minute structures lying in or upon the thyroid. In the human adult there are four in number each weighing about two grams. One pair is embedded in the medium dorsal surface of the thyroid and are, therefore, sometimes referred to as the internal parathyroids. The lower pair is situated between the equator and the lower tip of the thyroid. Some of the lower animals have six or more parathyroids which are found in a variety of positions throughout the neck and upper chest. The glands first appear at amphibian level and are found in all vertebrates.

The parathyroids were long thought to be insignificant bits of

thyroid tissue or small lymphatic glands. Hoskins (1933) states that they were first described by Remak in 1855, but that credit for their discovery commonly goes to S. V. Sandström of Upsala University, who published a clear picture of them in man and animals in 1880. He, too, regarded them as displaced, undeveloped fragments of thyroid tissue.

Although the first clinical description of tetany was made in 1815, the parathyroids did not attract attention until 1891 when Eugene Gley of Paris described them as independent organs. Then ten years later, MacCallum and Voegtkin proved that they control calcium metabolism and that their removal is followed by tetany. Before the recognition of the parathyroids as independent organs, some of the symptoms following thyroidectomy, which were in effect due to the simultaneous removal of the parathyroids, were attributed to the removal of the thyroid. The persistence of the idea that the endocrines exerted a detoxicating effect extended in the case of the parathyroids until as late as 1916 as evidenced by a statement by Gray (1916) which says: "The function of the parathyroids is supposed to consist in neutralizing toxic substances found elsewhere in the body."

The isolation and standardization of a powerful parathyroid extract called parathormone by Collip in 1925 and the association of hyperparathyroidism with generalized osteitis fibrosa cyctica in 1924 are, Rolleston (1936) claims, the outstanding milestones in the physiology and pathology of the parathyroids.

Relative to the present knowledge of the function of the parathyroids,

Hoskins (1933) states that these glands have been conclusively shown to have an important regulatory influence upon the metabolism of calcium and phosphorus. In addition and possibly by nature of their relationship to calcium metabolism, they play an important rôle in maintaining the nervous system in a state of optimal irritability. Similarly, Hoskins states, the responsiveness of muscular and perhaps glandular tissue to stimulation is regulated by their hormone.

Gonads

Early in the evolution of the higher forms the reproductive tissue was set apart from the body tissue in the form of gonads. One type of gonad produces the male cells, the spermatozoa, the other, the female cells or ova. In addition, the periodic changes in structure associated with the reproductive apparatus and the final attainment of sexual maturity are thought to be brought about through growth stimulating substances which arise in the germ glands, the testis and ovary. These glands, therefore, are not alone germ glands, in which the male and female germ cells are produced, but in addition are glands of internal secretion. Stockard (1931) states that the gonads seem to exert definite effects on important structural development during three different periods of life. During embryonic and foetal life, they seem to exert an influence on the development of the reproductive tracts; at puberty, the internal secretion exerts important influences in bringing about the development of secondary sex characteristics; and after puberty, they appear to exert an important rôle in molding the general type of growth and

development of the youthful individual.

The sex glands are different in structure and location in the male and the female. In the male, the testes, two glandular organs, are suspended on either side from the inguinal region by the spermatic cords and are surrounded and supported by the scrotum. Each gland weighs from eighteen and a half to thirty grams and consists of two portions, the testicle proper and the epididymis. The function of the testes already has been referred to, namely, the production of spermatozoa and an internal secretion which is essential for sexual growth and development. Hoskins (1933) states that the evidence is clear that the hormone of the male sex gland plays an important rôle in the normal development of the individual. The popular belief, however, in the relationship of the sex glands to the virility of the adult, he feels, needs more research although it is in a measure supported by scientific evidence. The rejuvenation experiments of Brown-Séquard with injections of sex gland extracts, reported before the Societé de Biologie of Paris in 1889, were an attempt to prove the relationship of the sex glands to general well being and virility in the adult male. As early as 1777 the connection was recognized by Bordeu who compared the castrated capon with the eunuchoid.

Though, from the eighteenth century, the gonads were vaguely thought to exert what is now recognized as an endocrine influence, and although the first experimental evidence of a hormonal function of any gland was demonstrated in the case of the testis by Berthold in 1849,

further scientific evidence of the exact nature of the testicular hormone is of quite recent origin. Butenandt is credited with being the first to isolate in pure crystalline form the male sex hormone which he called androsterone. This he achieved in 1931, not as others had attempted to do from the testicle itself but from human urine. Walker (1937) states that the reason that this should have happened so long after other organs of internal secretion had yielded their active principles was due to the small quantity of internal secretion within the testes at any time. T. C. Koch, he states, has estimated that to obtain one capon dose of testicular hormone anything from 50 to 100 grams of testicular tissue is required.

Hoskins (1933) states that the best evidence that the testis, early in the development of the organism, assumes the function of an internal secretion is derived from the observations of cattle breeders in the case of the free martin. Investigation has shown that twin embryo in cattle develop in different horns of the uterus but that the membranes fuse to form a common chorion; and that subsequent to this fusion, the blood vessels anastomose with the blood circulating through the two embryoes. This would have no particular consequence if the twins are both the same sex. If one is male and the other female, the latter is greatly modified, assuming the configuration of the male. The conversion of the female into an intersexual in this case is assumed by Lillie (1917) to be the consequence of earlier differentiation of the testes in the male embryo. The developing testes then produce the

male sex hormone which circulates through the female embryo and leads to a marked modification in the male direction.

The female gonads or ovaries are two small almond shaped glandular structures situated one on each side of the uterus in the posterior fold of the broad ligament, behind and below the Fallopian tube. Each ovary is attached by its inner end to the uterus by a short ligament and by its outer end to the Fallopian tube by one of the fringe-like processes of the fimbriated extremity. Each ovary weighs from three to seven grams.

The primary function of the ovary is to produce the germ cells for the perpetuation of the race. It also has the function of producing at least two hormones, oestradiol, from the interstitial tissue, which stimulates the proliferation of the glands of the endometrium and proliferation of the mammary glands, and progesterone, from the corpus luteum, which stimulates implantation and gland (aveolar) growth of the mammary glands and possibly relaxes the pelvic ligaments. It is not known at what stage the ovary begins to function as an endocrine organ. Frank (1929), whose work in this field is outstanding, believes that the hormone is not produced before birth.

In 1903 the rôle of the corpus luteum in the maintenance of pregnancy was established by Frankel. Leo Loeb in 1907 showed that the corpus luteum produced a hormone called progesterone. From 1912 on, numerous investigators have shown that extracts from the ovary and placenta contain a substance or substances which cause oestrogenic changes in the

uterus of castrated or immature animals. In 1923 the work on these oestrogenic principles was given a tremendous impetus by the development of a test for the qualitative and quantitative determination of these substances by Allen and Doisy. This test is known as the castrate mouse test.

Randall (1936) stresses the interrelationship of the anterior lobe of the pituitary and the female gonad and maintains that the function of the genital organs of the female must be initiated by the action of the gonadatropic hormone of the anterior pituitary on an organ capable of responding to such stimulation in a normal manner. As the Graafian follicles ripen, the stimulated ovary produces an oestrogenic hormone which causes proliferation of the endometrium. After the extrusion of the ovum and the formation of the corpus luteum, the latter body secretes progesterone, a hormone capable of stimulating further development and maturation of the endometrium producing pregrand endometrium. Randall states that for this process to be carried out normally the individual must have a general endocrine balance. He further remarks that a complete development of the uterus seems to be a necessary accompaniment.

The close functional relationship existing between the anterior pituitary and the ovary has led Zondek (1935) to refer to the pituitary as the "mater" to the ovary. Collip holds a similar view. Dickens and Brown (1937) say that the facts leading to this inference are that pituitary transplants lead to follicle growth and precocious sexual

development, while ablation of the anterior lobe of the pituitary causes failure of the follicles to develop, atresia of the follicles that have ruptured, atrophy of the uterus and vagina and non-development of the menstrual cycle.

Smith in 1925 and Aschheim and Zondek shortly after announced that the gonads, both male and female, remain dormant unless actuated by the secretion of the anterior lobe of the pituitary. Rolleston (1937) states that the interrelationship between the anterior pituitary and the gonads is reciprocal. Thus castration gives rise to cellular changes known as "castration cells" and the corpus luteum of pregnancy causes the formation of "pregnancy cells" in the anterior lobe of the pituitary.

Adrenals

As early as 1563, the adrenals were described by Eustachius who also described the canal which now bears his name. The first clue to the function of the adrenals or suprarenals was given by Thomas Addison of Guy's Hospital, England in his famous monograph "On Constitutional and Local Effects of Diseases of the Supra Renal Capsules", published in 1855. Addison was able to show that the destruction of the adrenals, to which the symptoms described in his monograph were due, is commonly caused by local tuberculosis.

Addison's monograph aroused the interest of the physiologist, Brown-Séquard who began a series of experiments in which he removed the adrenal glands of dogs, cats, rabbits, and guinea pigs. The operation

resulted in symptoms similar to those noted in Addison's Disease, marked prostration followed by death, thus indicating that the adrenals were essential to life. Brown-Séquard, however, ascribed the fatality to toxemia, feeling that the poisons actually produced in the body were no longer neutralized or removed by the adrenals. Brown-Séquard's work was for a time discredited by the findings of two investigators who used white rats as their subjects. The rats survived the operation and continued to live in excellent health. The logical conclusion was that the results obtained by Brown-Séquard were due to surgical intervention and not to the loss of the adrenals. The fact that white rats have enough accessory adrenal tissue to be able to dispense with the glands proper was not recognized until a later date. The hypothesis that the adrenals glands exerted a detoxicating effect was not abandoned until after 1894 when Oliver and Schäfer, by experimental injection of extracts of adrenal, discovered that the glands have as their function the formation of a hormone that affords tonus to the circulatory system.

Hoskins (1933) credits John J. Abel of John Hopkins University with being the first to discover in the adrenal medulla the pressor substance from which the hormone was isolated simultaneously by Aldrich and by Takamine in 1901. Adrenaline, as the hormone of the adrenal was called, has often been called the "emotional hormone" because its output varies in fear, anger, love, and joy. Hoskins states that it is to Crile's and Cannon's continued research that we owe much of our understanding of the adrenals.

The active principle of the cortex, called "cortin" by Hartmann in 1928 and "eschatin" by Swingle and Pfiffner in 1930, has been found to have an influence on growth. Cortin influences the distribution of sodium potassium and chloride in the blood and tissues. It also affects the volume of the circulating blood and the metabolism of sugar. Gregory (1935) states that both the cortex and medulla function in heat regulation to enable the organism to adapt rapidly to changes in temperature.

The adrenal glands in man consist of a pair of organs located in the upper pole of each kidney to which they are closely adapted. By reason of their location in the human body, they are often called the suprarenals. In other animals and primates, who continue to walk on all fours, the term addrenals, Hoskins (1933) states, is more appropriate as they lie ahead rather than above as the name implies. The glands consist of a medulla and cortex and, in an adult man, the two adrenals combined weigh a trifle over one-fourth of an ounce. The adrenals are scantily represented below the higher animals, the known exceptions being a few invertebrates in which glands have been discovered that yield an extract somewhat resembling the product of the adrenals. Beginning with the fishes and extending up to man, the adrenal glands are an important part of the glandular system.

The recognition of the functional interrelationship of the adrenals and the gonads seems fairly well established. Carr and Cameron report that there seems definite evidence that adrenalectomy produces in male rats loss of libido and potency and degeneration of the seminiferous

tubules, and in ninety percent or more female rats suppression of the oestrous cycle and atrophy of the ovaries. In the latter, the cycle can be restored by homotransplants of adrenal cortex or by injections of cortical extracts (Cameron 1935). Cameron (1935) states that in agreement with these findings, it is recognized that in Addison's disease, amenorrhea, absence of libido, impotence and atrophy of the testes may occur, while treatment with cortical extract tends to produce a return to normal function.

Hoskins (1933) states that the fact that the adrenal cortex is at its relatively maximum size during the early foetal period when growth and development constitute the major activities of the organism suggests that it plays an important rôle in connection with such processes. He further states that it has been noted that a lessening of cortical activity occurs during pregnancy and during the breeding season when special demands are placed upon the organism.

Pancreas

The pancreas was known as a digestive gland a number of years before it was recognized as a gland of internal secretion. Discovery of the digestive function of the pancreas was made by Claude Bernard in 1846. A description of the islets in the pancreas was made by P. Langerhans in 1869 and named after him in 1893 by Leaguesse who, with Hedon in the same year, concluded that the islets provided the internal secretion. Von Mohring and Minkowski in 1889 had shown the existence of this secretion

through the experimental production of fatal diabetes by the pancreas. In the next twenty years there were several attempts to treat diabetes mellitus by pancreatic extracts, but they were attended by such severe reactions because of the protein content of the extracts that they were abandoned until a protein free extract was obtained by MacLeod, Banting and Best of Toronto, Canada in 1922.

Interspersed among the lobules of the glandular tissue of the pancreas are numerous inclusions called the islets or islands of Langerhans. These islets or structures that resemble them are found in all vertebrates from fishes up to man. They differ consistently in relative size and number. In fishes the island tissue constitutes a single mass. The function of the islets is the production of a hormone which affects the carbohydrate metabolism by regulating the amount of sugar in the body.

Thymus

The thymus, consisting in the human animal of two large masses of glandular tissue, is located in the anterior mediastinum, and the greater portion of gland lies behind the manubrium and body of the sternum. The size and weight of the gland-like organs vary considerably. It increases in size with the time of puberty when it undergoes involution. Brown (1927) states that the involution of the thymus seems to be accompanied by a partial involution of the lymphatic tissue throughout the body which is reflected in the blood picture. The gland is relatively larger in castrated than in normal animals which is also true in man

according to Tandler and Grosz (Engelbach 1932a--Vol.2). The gland is said to decrease in size during pregnancy.

In lower animals the thymus is found as far down in the scale as primitive fishes. Hoskins (1933) states that according to Cowdry the thymus may be regarded as the descendant of a gland that originally poured its secretion into the alimentary canal but which has since undergone a transformation of lymphoid type of tissue as other vestigial organs have a tendency to do.

Our knowledge of the physiology of the thymus dates from Friedleben in 1858 who found that it was not indispensable to life and was concerned in some way with blood function and with nutrition and growth. In 1908 Basch demonstrated that it was concerned with the calcification of bones and suggested its importance at the younger age level. An important series of studied were carried on by Klose and Vogt between 1910 and 1914 which indicated that thymectomy in young dogs resulted in adiposity, subsequently in cachexia and finally in death.

In addition to its influence on general skeletal growth, it is reported to have an effect upon gonadal growth. Calzolari, as early as 1898, believed that there was a close relationship between the thymus and the reproductive organs. When his theories were put to experimental test, he found that the thymus was larger in a series of castrated male rabbits than in normal animals of the same age. He concluded that the removal of the testes cause a delay in the regression of the thymus that normally takes place about puberty. His results were reenforced

by Henderson who worked with rabbits, guinea pigs, and cattle (Hoskins 1933). Hoskins (1933) states that evidence such as this has led the well known British authority, Swale Vincent, to conclude as follows: "It would appear that the normal involution of the thymus is due to the development of the reproductive organs, though this cannot be the only cause. The experiments, further, tempt one to the hypothesis that the thymus furnishes an internal secretion of some kind which ministers to the needs of the economy before the reproductive organs are fully developed. Normally, the internal secretion is provided by the testes (or ovary) after puberty, but if castration is performed, the thymus maintains its original structure and function. This internal secretion must, of course, be of different nature from that which determines the development of secondary sexual characters as these do not become manifested in castrated animals."

Hoskins states that, more and more, researches of recent years have continued to cast doubt upon the standing of the thymus as a member of the endocrine system. Gregory (1935) confirms this statements, saying that at the present time the concensus of opinion is that the thymus is not an endocrine organ. Bonar (1935) likewise states that after years of study Hammar was unable to prove that it produced an internal secretion, and up to the present time (1935) no one else has been able to do so in the human at least. Painstaking expiration studies in dogs led Park and McClure (1919) to conclude that the thymus is not essential to life. Bonar further states that, in general, most observers agree

that thymectomy is not followed by detectable symptoms. Rowntree, Clark and Hanson (1935), on the other hand, found an accruing acceleration in growth and development in five generations of rats under continuous treatment with thymus extract, thus indicating that in some way the thymus has an effect upon the functions of the body.

Perhaps the most convincing evidence yet secured of an hormone function of the thymus is that of Oscar Riddle's in regard to ovulation. Riddle discovered that pigeons frequently laid eggs that are deficient in the shell and the albumen layer that surrounds the yolk. An autopsy of such birds revealed defective thymuses. Riddle further discovered that feeding dried thymus substance to pigeons thus affected resulted in restoration of the ability to produce normal eggs (Hoskins 1933). Hoskins states that such an experiment meets the specification of the physiologist Pfeuffler who feels that the proof of an internal secretion is that, in the absence of normal function, resumption of the same takes place on the administration of extracts or implants of the gland.

Pineal

Situated above and behind the third ventricle of the brain, the pineal body or epiphysis is a small grayish body. In early life, it is glandular and attains its maximum growth about the seventh year. After this period, and particularly after puberty, it decreases in size and the glandular tissue is replaced by fibrous tissue. The pineal is more highly developed in many of the lower vertebrates than in man.

There is actually little known about the function of the pineal at the present time. Zondek (1935) states that many theories have been propounded but that no conclusive statement can yet be given. It has not been definitely established whether it produces an internal secretion. Zondek states that, according to Mauberg, it probably does. Brown (1927) favors the idea that it does not produce an internal secretion because it belongs to an entirely different system from the other glands of internal secretion, it being a vestigial eye instead of a nephridium. He feels that it may exercise an inhibitory effect directly through the central nervous system rather than by a chemical means. Brown's theory that the pineal is not an organ of internal secretion is the one that is generally accepted.

Zondek (1935) feels that the best grounded view is that the pineal body inhibits the action of the sex glands. He reports the findings of various authorities as follows: Sarteschi reported in 1915 that in rabbits and dogs extirpation of the organ was followed by testicular hypertrophy and obesity. Horrax observed that in young guinea pigs, epiphysectomy caused gain in weight and growth of the testicle and seminal vesicle; Foa obtained similar results in cockerels and Jolcob reported increased growth of their combs and whole body; Izawa found that in rats that had been epiphysectomized at the age of twenty days, the ovaries, two months afterwards, were about twenty percent heavier than in the control group; Renton and Rusbridge, on the other hand, found that removal of the pineal produced no change in the sex

glands of either male or female. According to Fleishman and Goldhammer, the pineal suppresses the function of the sex glands, especially oestrus. Black and Hulles, Vercellana and Aschner claim that castration in cats, dogs, rabbits, and cattle is followed by atrophy of the pineal body. The diversity in these findings has led Zondek to conclude that the problem is yet unsolved.

The cooperative relationship of the thymus and the pineal in controlling the rate of growth and maturity has been suggested by several authorities. Rowntree states that the pineal and thymus may balance each other in controlling the rate of growth and maturity (Gregory 1935). Brown (1927) claims that these two structures, one acting through the central nervous system, the other through the haemopoietic system, definitely delay maturity in the interest of the somatic growth of the individual.

The doubtful position of both the thymus and the pineal in the endocrine system does not warrant a further discussion of them except to mention two important experiments from the point of view of their effect upon the offspring of the subjects used in the experiments. Rowntree, Clark, Steinberg and Hanson (1935) found that the administration of thymus extracts to rats caused acceleration of the rate of growth and development and hastened the onset of adolescence in the offspring of treated rats. Thymectomy in parent rats, on the other hand, retarded the rate of growth in the young as indicated in the weight curves. Administration of pineal extract retarded the rate of

growth, accelerated the rate of development and hastened the onset of adolescence in treated rats. The injection of succeeding generations of parent rats resulted in the amplification of the effects of the thymus and pineal extracts.

Endocrine Dysfunctions and the Rôle of Inheritance in Their Etiology

The causative factors of endocrine dysfunction are both endogenic and exogenic. According to Engelbach (1932a--Vol.1) the relative importance of these factors in disorders of the endocrine glands is the reverse of that existing in the production of disease of non-endocrine systems. Engelbach states: "The endocrine glands primarily derive their morphology from inherent qualities transmitted from the progenitors. Morbidity resulting from incretory disorder is primarily of endogenous origin. On the contrary diseases of other systems result mostly from postnatal exposure to environment. The fundamental purposes of incretory function are: (1) tissue differentiation; (2) emotional development; (3) physiologic action; (4) provision for procreation. Acquired diseases produce structural changes or functional derangement in the organs thus developed and activated. Ordinarily the extrinsic exciting cause of acquired disease of non-endocrine systems are recognized as the most significant etiology while intrinsic predisposing factors derived from inheritance are considered of minor importance. In contrast, the inherent influences are of first importance in the production of endocrine abnormalities."

Engelbach further states that parental incretory defectiveness may result in either a positive or a potential endocrinism in the offspring. "The infant having a potential incretory disorder is more predisposed to disturbed functions of the glands of the endocrine system than the infant born with normal endocrine balance. This predisposition is

usually augured by endocrinism in the family history as goitre or obesity. The trait may be manifested by what is usually considered an unimportant familial trait, such as underheight or amenorrhea, yet is sufficient to indicate the gland in the offspring which will be most susceptible to exogenous causes of endocrine disorder." Engelbach substantiates these statements by the findings of a study of 2098 endocrinopathies in which non-endocrine disease had been excluded by searching and prolonged observation. Of the 2098 cases studied, a family history was obtained in 1910 cases. In 410 cases or 21 per cent a positive history of familial endocrinism directly related to the disorder of the patient was found. The number, Engelbach feels, is probably materially reduced by the difficulty in obtaining accurate information in some cases and by the neglect of the investigators to make a careful inquiry in the earlier cases of the study. An analysis of the 1910 cases, in which a family history of endocrinism was found, showed that of the total of 414 thyroidism, 47 or 12 per cent had a positive family history; and that in 596 pituitarism, 170 or 29 per cent submitted unquestionable evidence of endocrine disorders in the family. One hundred and seven or 32 per cent of the 737 biglandular cases gave a family history of thyroid, pituitary or both, and of the 556 cases of gonadism, 63 or 15 per cent had a family history of endocrinism. In addition to the direct transmission of uniglandular or biglandular disorders, the family histories in some cases, Engelbach states, contained evidence of disorder of other glands such as pancreatic diabetes which is probably interrelated with the function of one or more glands as the thyroid,

pituitary, or gonads.

Gordon (1935) places the incidence of familial endocrinopathies between ten and twenty per cent.

Fridenberg (1922), in discussing disorders of metabolism and internal secretion in relation to the eye, states: "The influence of individual glands of internal secretion on processes of heredity are not fully understood, nor is it known whether definite dyscrinisms are transmitted in the germ plasm and chromosomes, so that it is not possible to refer this or that ocular malformation or developmental arrest to one or the other endocrin origin. The relation of the endocrin hereditary factors becomes interesting and suggestive in ophthalogy because of the morphological and clinical similarities and analogies between certain disease manifestations on the one hand and individual racial characteristics of purely physiological significance on the other. Thus the Mongol fold or epicanthus which is a normal heritage of the Chinese child and a stigmata of marked constitutional degeneration in a Caucasian is in both an evident endocrin marking which is logical to assume is of uniform provenience."

Zondek (1935) makes this statement in regard to the possibility of an inheritance factor in endocrine dysfunction: "Many indications point to the view that anomalies in the make-up of the endocrine system are transmitted to the offspring, the same hormonal organs showing deviations from the normal state in the child and in its mother. We may allude to experimental investigations by A. Seitz: he found that

in the offspring of thyroidectomized rabbits, the pituitary gland was very often hypertrophic both in its relative size and histological character of its cellular components; in the young animals whose adrenal glands had been removed, the thymus and the spleen follicles were enlarged. One may therefore assume that in the organism of the foetus or child a deficiency in the maternal supply of certain hormones is compensated by the production of other hormones, and this leads to hyperplasia of the corresponding glands. Similar processes undoubtedly occur in persons unprovided with or deprived of, one or the other hormonal gland; in my opinion hyperplasia of the hormonal glands should be considered as one of the principal reactions to certain cellular changes." Zondek further states: "It is a matter of common experience that diseases which are generally attributed to alterations in the endocrine organs show a particularly high incidence in some families: thus on questioning patients suffering from goitre, Graves' disease, excessive obesity or other anomalies of internal secretion, identical or similar conditions are often reported to exist in their ancestry or among their side line relations. From the standpoint of clinical endocrinology the mystery of the predisposing factors must urge us to study heredity. Research has here a domain presenting extensive possibilities for the future. Whether, in addition to the known heredity laws of general pathology, there may be discovered or even exist others limited to hormonal diseases, the future will show."

Mohr (1934) says: "That endocrins in hormone animals may form an

important link between genes and characters becomes daily clearer." He elaborates on this statement by saying that when one sees a family with two homozygous excessive midgets, a pair of identical chondrodystrophic twins or hereditary cases of oesteopsothyrosis or of adipositas one can hardly doubt that hereditary dysfunction of endocrine glands is involved. Mohr further states that a steadily increasing number of parallel mutations in domesticated and laboratory animals are now accessible to experimental and embryological analyses. Landauer and Dunn, Stockard, P. E. Smith and MacDowell, Bouverie, Begg and others, he states, are engaged in investigations that may give us insight into the single steps in the pathogenetic processes leading to analagous states in man. In Stockard's laboratory, he claims, he has seen histological preparations from endocrine glands of dogs suffering from different hereditary anomalies which, in many respects, correspond to analogous abnormalities in human beings.

Stockard (1931) of Cornell Medical School, who has done considerable work with dogs, states: "When we examine the structure and shapes of modified animal types, we often observe conditions closely similar to peculiar growth reactions known to result from disturbances and deficiencies in endocrine gland secretion. We might, on this account, attribute some of the freak types to deviations or diseases in the glands of internal secretion. On further study, we find that the strange type is actually of genetic origan, a mutant or sport; nevertheless the primary effect of this mutation is the production of a

peculiar deviation in glandular development. And these glandular deviations are directly responsible elements in bringing about the peculiar freak development which is the noticeable end results of the primary gland mutations. Thus, for example, one might think that the bulldog inherits his grotesque form and appearance as such, while, as we interpret it, he inherits a definite abnormality of internally secreting glands and these defective glands act as secondary causes of the bulldog pattern." He further states: "Practically all of the peculiar dog breeds have been derived through hybridization and it may be due to the crossings that so many germinal mutations and sport-like forms have appeared. When odd types began to occur, the breeders carefully isolated and preserved them in order to bring about the artificial races. Many of the breeds exhibit some form of structural distortion which may be associated with strange and widely modified complexes of the endocrine glands. The breeders, of course, may have been entirely ignorant of the basis of the selection. They may have chosen specimens solely on account of their strange forms which could be readily observed. But in many cases the form was only the symptomatic expression of the distorted growth controlling complex of internal secretions which lay behind the situation. And behind all this were the genetic mutations which gradually became purified through selective breeding."

A statement, which would strengthen Stockard's theory, is made by Gowen (1937). It is as follows: "Chemical agents, hormones, viruses utilized as initiating agents for tumors are significant to us

as the physiological effects that they produce may put them in the category of agents affecting somatic segregation, aberrant mitosis or gene mutation."

W. E. Castle (1938) says that as far as he knows there is no direct evidence as to inheritance as a result of endocrine dysfunction in man, but states that it is probably similar in man and other mammals. To substantiate this point of view, he cites the case of hereditary dwarfism in mice that has been worked out by Dr. George O. Snell of Jackson Memorial Laboratory, Bar Harbor, Maine. This case of hereditary dwarfism was due to dysfunction of the pituitary gland. It is inherited, he states, as a simple recessive character. Animals pure bred or homozygous for the character are undersized and sterile, but if given implants or injections of normal pituitary, they grow to normal size and reproduce.

Beck (1922) says relative to the pituitary disorder, dystrophilia adiposogenitalis: "There is unquestionably an inherited tendency in certain families toward the development of endocrinopathies which to some extent follows the Mendelian laws."

Dr. George V. Smith (1937) of the Fearing Research Laboratory, Brookline, Massachusetts states that Dr. Priscilla White of Boston has pretty definitely shown that there is a genetic factor in certain cases of diabetes mellitus. Other workers, such as Macklin and Joslin, hold a similar view.

Robert C. Cook (1937), Editor, The Journal of Heredity, reports that genetically controlled defects of the thyroid are probably the basis of

cretinoid "bulldog" calves in cattle.

The possibility of the endocrine glands of the mother influencing the development and growth of the offspring is now fairly well established. Schlapp (1923) says: "Recent studies of mental defective children and their mothers have served to emphasize the fact that prenatal pathological conditions in the female parent are responsible for certain malformations in the child. These investigations have thrown light upon conditions of many obscure defects and deformities. More specially, they have proved for the first time that to certain chemical imbalances in the blood of the mother can be traced the causes of many of the strange and monstrous malformations." He goes on to say that for some years we have understood from laboratory experiments on lower animals that the introduction of extrinsic poisons in the female parent will bring about weaknesses, abnormalities and monstrosities in the offspring, but that it is only recently that we are beginning to realize that internal factors having to do with disturbances of the ductless glands are the chief causes of the malformations in children. Schlapp further states that such malformations have been particularly baffling in view of the fact that the parents in many cases are apparently healthy individuals who revealed none of the stigmata so badly evident in the progeny.

Hoskins (1933) is somewhat more cautious in his statements in regard to the influence of the internal secretions of the mother on the offspring, for he says: "Relatively little is known regarding the

influence of hormones on the organism before birth. The developing infant obtains its sustenance from the blood stream of the mother. The placenta is permeable to hormones as it is to all of the various substances that go to make up the growing body. The endocrine system in the mother as well as in himself, therefore, undoubtedly influences the development of the child."

Recent experiments by Tanioka (1936) and Watts (1935) show the effect of acceleration and diminution of the activity of the various glands of the mother on the offspring. In a series of experiments, made for the purpose of demonstrating the effects of functional disturbance of the maternal endocrine glands on the genital gland of the female fetus, Tanioka showed that in each case, using the pituitary, thyroid, pancreas and suprarenals, an effect on the genital gland of the female foetus was observable. In Watts' experiment, daily injections of beef anterior lobe preparation and phyone was made on female rats. The effect noted was an increase in the weights of the new born delivered at full term over those of the control group, and similarly, over the offspring born of the same mothers at a previous pregnancy. The studies by Rowntree, Clark, Steinberg and Hanson (1935) already have been referred to.

The possibility of somatic changes as a result of disturbance of the maternal endocrine balance seems, therefore, fairly well established. The possible effect of hormonic action on the gamete is more difficult to explain.

As early as 1895, Yves Delage in discussing the possibility of the transmission of somatic modifications pointed out how changes affecting the soma produce an effect on the ovum. Delage wrote: "Ce qui empêche l'oeuf de recevoir la modification reversible c'est qu'étant constitué autrement que les celles differenciées de l'organisme il est influencé qu'elles par les mêmes causes perturbinces. Mais est-il impossible que malgré la différence de constitution physico-chim que il sort influencé de la même façon?

Commenting on Delage's statement, Cunningham (1921) feels that Delage's meaning would probably have been better expressed if he had written 'ce qui paraît empêcher, for, he states, by "modifications reversible" he means a change in the ovum that will produce in the next generation a somatic modification similar to that by which it is produced. Delage argues that if the egg contains the substances characteristic of certain categories of cells of the organism, it ought to be affected at the same time as those cells and by the same agents. Cunningham states: "He thinks that the egg only contains these substances or the arrangements characteristic of certain general functions (nervous, muscular, perhaps glandular of divers kinds) but without attribution to localized organs. In his view there is no representation of parts or of function in the ovum, but a simple egg and the categories of cells which in the body are charged with the accomplishment of the principal functions. Thus mutations of organs formed of tissue occurring also elsewhere in the body cannot be hereditary but if the organ affected contains the

whole of a certain kind of tissue such as liver, spleen, kidney, then the blood undergoes a qualitative modification which reacts on the constitution of the egg." Cunningham interprets Delage's statement by saying: "Suppose the internal secretion of a gland (e. g. glucose from the liver, glycolytic ferment from the pancreas) is the physiological excitant for the gland. Then the gland, if suppression is partial, will undergo a diminution of activity. But in the eggs the specific substance of the gland will also be less stimulated, and in the next generation a diminution of the gland may result."

Cunningham, later in his book, "Hormones and Heredity", in expressing his own ideas, says that the facts concerning the action of hormones are beyond the scope of current conception of the action of factors or genes, localized in the gametes and particularly in the chromosomes, whereas he feels that, in certain cases, the development of organs or characters depend on a chemical substance secreted in some distant part of the body. To quote Cunningham: "It was formerly stated that no process was known or could be conceived by which modifications produced in the soma by external stimuli could affect the determinants in the gametes in such a way that the modifications would be inherited. The knowledge now obtained concerning the nature and action of hormones shows such a process actually exists and in modern theory real substances of the nature of special chemical compounds take the place of the imaginary gemmules of Darwin's theory of pangenesis or the "constitutional units of Spencer"." Thus by direct and indirect implication, Cunningham

suggests that hormones could influence the germ plasm.

Vernon cites instances of the cumulative effects of changed conditions of life and points out that they are not really instances of the cumulative effects of changed conditions but merely of germ plasm and body tissue being simultaneously affected, and states that the only conceivable way for the environment to act on the germ plasm is by means of a chemical influence through products of metabolism and specific internal secretion (Cunningham 1921).

Keith considers that, as far as possible, nature seems to have safeguarded the progeny by isolating the gonads from the functional influence of the parental body. He agrees, however, that the germ plasm can be injured by toxic substances from without (Langdon-Brown 1927).

Brown (1927) offers the following explanation of the effect that hormones may have on the gamete: "The germ plasm of the two sexes, prior to fertilization, extrudes some of its nuclear substance. The great advantage of this is that, on fertilization, there is a recombination of the genes; thus favorable mutations can arise which facilitate evolutionary change. Whether the discord is from the strong or the weak suit, so to speak, must undoubtedly influence the make-up of the offspring. It does not seem beyond the bounds of possibility that the autonomic nervous system acting through the endocrine glands may play a part in determining the discord."

Fridenberg (1922) states: "Sex and other processes of heredity are

endocrin reactions linked to chromosomes (Goldschmidt). The fertilized egg protoplasm furnishes the chemical material for growth and differentiation while the chromogen furnishes determinants and factors for specific direction of processes which make offspring resemble their progenitors. These factors are enzymes of specific characteristics in quality and quantity concentration. The velocity of the enzymes, which is proportional to their concentration, stabilizes the rhythm of differentiation. The principal reaction thus accelerated by enzymes of heredity to a definite velocity is the function of hormones directing growth, differentiation, periodic development with an action similar to that of the glands of internal secretion."

The idea of an hormonic action of the mother on the offspring is refuted by Baur, Fischer and Lenz (1931). Referring to maternal impression on the offspring, Lenz says: "Since the doctrine of "internal secretion" has become fashionable, we have often been assured that hereditary modifications must have arisen in this way, - which is piquant. The readiness with which laymen are apt to adopt such views uncritically and amateurishly is in reverse proportion to their capacity for forming any clear ideas of processes in question. The actual connexion between hereditary equipment and processes of internal secretion is, not that the internal secretions modify the hereditary equipment, but conversely, that the organs of internal secretion themselves originate as part of the hereditary equipment. As Morgan puts it, internal secretion is one of the ways in which the hereditary equipment takes effect."

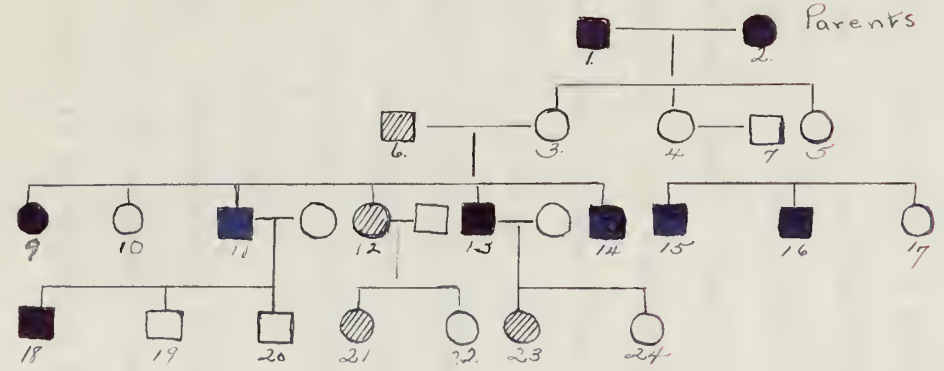
Julius Bauer (1932) holds a similar point of view. He feels that many authors confuse the inherited characteristics of a being determined potentially at the moment of fertilization with its acquired characteristics. In other words, they fail to differentiate between characteristics of genotypical origin with those of phenotypical basis. Many pathological conditions, he feels, are not understood without a profound knowledge of human genetics. He cites as an example of this the so-called Laurence-Moon-Biedl syndrome which most endocrinologists attribute to a disturbance of the pituitary gland and which most of them feel is inherited. Bauer, on the other hand, feels that the retinitis pigmentosa, which is present in this syndrome, is a pure genotypical disease produced by a pathological recessive gene just as the polydactylism and syndactylism are genotypical pathological conditions. He feels that there is little doubt about the fact that we are dealing here with a more or less typical combination of several abnormal genes due to the fact that these genes are localized in the same chromosomes. The Laurence-Moon-Biedl syndrome, he maintains, is a typical example of linkage of genes. Bauer further questions whether the obesity and hypergenitalis, which are associated with the retinitis pigmentosa and polydactylism in this syndrome, are attributable to an endocrine disturbance. Only a small per cent of the cases of endogenous obesity, he states, have their origin in clinically detectable disturbances of the glands of internal secretion. Most of these cases, he claims, can be explained by a constitutional anomaly, that is, they originate from an abnormal gene bringing about a constitutional tendency of the tissues to store fat on account of some anomalies in the intermediate metabolism.

The glands, he states, are undoubtedly influenced by the gene or genes producing obesity, but they are only one means used by these genes or their phenotypical manifestations.

Furthermore, Bauer claims that symptoms of abnormal functioning of some of the endocrine glands or a particular disposition to a pathological process in some of them are found in cases of obesity, when actually the obesity is not the consequence of an endocrine disorder. Frequently, he states, in patients with constitutional obesity, there are concurrent symptoms of gonadal difficulties and other signs of what he terms "endocrine stimatisation" which may indicate the biological inferiority of the endocrine system associated with obesity. Such an accumulation of constitutional abnormalities in an individual represents what Bauer terms, a "status degeneratious". Representatives of status degeneratious, Bauer claims, are frequently, but erroneously, diagnosed as endocrine cases.

The attached chart (Figure 1) is intended by the author to illustrate the hereditary character of endocrinopathies. According to the author's interpretation, it is illustrative of endocrinopathic heredity and shows the consistency with which endocrine disorders appear in so-called "tainted" families. Bauer's interpretation would probably be that the individuals or offspring are suffering from a constitutional anomaly which might be reflected in endocrine disturbances.

From this discussion, it is clear that there is little agreement among authorities as to either the etiology of endocrine disorders or the rôle of inheritance in this etiology. Further discussion of the



1. Giant
2. Diabetic
6. Dyspituitaric
9. Exophthalmic Goiter
11. Hurelip
12. Dyspituitaric
14. Congenital Blindness
15. Moderate Giant
16. Giant
18. Osteomalacia and Dwarf
21. Hyperpituitaric

Females — Normal; Abnormal tendency; Abnormal — Males

Figure I: Illustrative chart showing endocrinopathic inheritance

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subject will be pursued under the headings of the various glands and may tend to throw more light on the subject. No attempt will be made to cover all the conditions ascribed to endocrine dysfunction or to present all of the evidence in regard to the hereditary nature of these conditions.

Pituitary

The activities of the pituitary express themselves differently in childhood and adult life. In childhood, the pituitary is concerned principally with growth. With the onset of puberty, it becomes closely associated with gonadal development. That the pituitary is concerned with growth and sexual development has been shown by Cushing and Aschner. Cushing, in 1901, succeeded in removing a large portion of the anterior lobe in dogs and in keeping them alive. The result was that the animals became unusually fat and suffered a regression of the sexual organs as well as the thyroid gland. Similar results were obtained by Aschner at about the same time. This investigator, who worked chiefly with puppies, emphasized the arrest of growth that ensued. The skeletons persisted in the infantile state as did also the sex organs.

Hyperfunction of the Pituitary: Certain conditions associated with hyperfunction of the pituitary are now recognized. Those which are connected with overactivity of the anterior lobe are gigantism, acromegaly and Cushing's basophilism.

Gigantism: Gigantism is a condition found in preadolescence which is characterized by an abnormal growth of the long bones. Rolleston (1936) states that it is caused by adenomata of the eosinophile cells

and that associated with the overactivity of the pituitary is an enlargement of the thyroid and chromophil cells, adrenal glands, and perhaps other glands. Hoskins (1933) states that deficiences in the sex function are also rather characteristic of giants, possibly due to a disturbance of the gonadotropic hormone of the pituitary. Engelbach (1932a--Vol.2) apparently disagrees with Rolleston, for in defining gigantism, he says that it is an abnormal overgrowth of the entire body caused by excessive function of the anterior lobe of the hypophysis, unrelated to tumor. The overdevelopment of the osseous system, he claims, is due to hyperosseogenesis of both the epiphyses and periosteum, and that the skeletal overgrowth attained during adolescence remains permanent through life, although in many cases, the hyperactivity changes to inactivity. Simpson (1937) states that gigantism may be due: (1) to an excessive secretion of the growth hormone before the epiphyses unite; (2) to a delayed union of the epiphyses (eunuchoidism), a normal amount of the growth hormone thus being permitted to act over an abnormally long time; (3) to a combination of 1 and 2.

Individuals with gigantism reach an abnormal height, ordinarily attaining six and one-half to eight and nine feet. The New York Times (1937) recently reported the case of Robert Wadlow, who at the age of eighteen had reached a height of 8 feet 4 inches and a weight of 390 pounds. Lisser (1928) emphasizes that in true gigantism the abnormal tallness originates in childhood (Hoskins 1933). Hoskins (1933) states that the condition is rare.

Acromegaly: Similar in principle and identical to gigantism, as far as is known in its fundamental metabolic manifestations, is the condition of acromegaly. Some authorities refer to acromegaly as gigantism in the adult. Hoskins (1933) states that it differs from gigantism essentially by the fact that the body has so matured at the time of onset as not to be capable of further symmetrical development, and that the superabundance of tissue, that is produced under the stimulating action of the growth hormone, is therefore confined to those parts of the body that are still able to respond to stimulation. Such parts are the skin, hands, and feet. Much the same idea was held in 1895 by Brissaud and Meige who argued that gigantism is acromegaly during the period of growth whereas acromegaly is gigantism of the adult. In the same year Woods and Hutchinson suggested that gigantism is acromegaly beginning in foetal or early life. Rolleston (1936) states that the now accepted idea of the relationship of acromegaly to gigantism was expressed by Lannois and Roy in 1903 to the effect that hyperpituitarism causes giant growth before and acromegaly after the epiphyses have united. Experimental acromegaly was produced by injections of anterior pituitary in rats by Evans and Long in 1921 and in dogs by Putnam, Benedict and Teel in 1929 (Rolleston 1936), thus proving its connection with anterior lobe activity.

Acromegaly begins most commonly in early middle life. It may exist in any stage from the barely perceptible to that in which the victim becomes a caricature of his former self. Hoskins (1933) says

that minor degrees of acromegaly are not uncommon. The condition is manifested by enlargement of the hands and feet and of the bones and cutaneous tissue of the face and by splanchnomegaly. Simpson (1937) states that the pituitary is usually although not necessarily enlarged and on section, eosophile adenoma is found in the anterior lobe. The adrenal cortex is hyperplastic and multiple adenomata may be present. The thyroid is enlarged in fifty per cent of the cases, the usual change being an increase of adenomatous colloid. Accompanying changes in the form of enlargement and adenomatous hyperplasia may be present in the parathyroids and the pancreas. The ovaries and testes are usually atrophic.

Although a somewhat unusual disease, acromegaly is not rare. Bassoe (1922) states that it shows no tendency to special geographical distribution such as is found in certain thyroid conditions or to selection according to race. Bassoe reports that Osler is quoted as saying that it occurs rather more frequently among women than among men and that a similar point of view is held by Levi. Rolleston (1936) states that during pregnancy slight changes suggesting a mild degree of acromegaly occasionally occur and has been thought to be due to pituitary enlargement. Hoskins (1933) attributes this condition at such a time to an overactivity of the pituitary in the interest of the developing embryo.

Acromegalic Gigantism: A condition of gigantism and acromegaly may exist simultaneously in the same individual. Cushing in 1912 pointed out the difficulty in knowing where gigantism ends and acromegaly begins. Relative to the occurrence of gigantism and acromegaly and a combination

of the two, Hoskins (1933) says: "When the activity of the pituitary begins before puberty the result is symmetrical over-development of the body, that is gigantism. If it arises at the time of adolescence, the intrusion of the gonad hormones serves to modify the developmental processes, and what is started as gigantism may continue as acromegaly (acromegalic gigantism). If still further deferred to the early twenties, pure acromegaly results. Hoskins states that the onset of acromegaly seldom takes place after the fortieth year, although it has been reported by some workers in children.

Because of the similarity of these two conditions, gigantism and acromegaly, discussion of the rôle of inheritance in their etiology will be undertaken simultaneously.

Zondek (1935) states that gigantism sometimes is hereditary, basing this statement on the fact that he knew a family in which three grandsons of an abnormally large woman were all afflicted with gigantism. He further states, however, concerning the origin of gigantism as of all forms of growth disturbances, that it should be borne in mind that in some cases the hormonal system may be perfectly normal. Such cases, he states, should be attributed to germinal malformations or, in the words of Julius Bauer, to autochthomic chromosomal disorder.

Referring to the causes of gigantism, Simpson (1937) states that there is probably the additional factor of an inherent capacity of the bones to respond to the stimulus of the growth hormone. Gigantism, he claims, tends to run in families and to be common among certain races, for example, the Swedish race.

The family history of a case of hyperpituitarism recently recorded by Behrems and Barr (1932) showed no marked tallness in the ancestors and no endocrine disorders. This, however, does not necessarily discredit hereditary endocrinism as a causative factor in gigantism for Zondek (1935) states that according to a classification of Von Langer one may distinguish between healthy and morbid gigantism. The great majority, Zondek claims, belongs to the second class since in the majority of cases the abnormal development is due to an hormonal disturbance of growth.

Rolleston (1936) states that Marie stoutly denied that acromegaly was hereditary, but Verstuceten in 1889 and von Recklinghaussen in 1890 inclined to the opposite opinion. Rolleston further states that Atkinson in 1932 collected about a dozen examples of hereditary or familial incidence, and Curschmann and Schipke in 1934 and Lewis in the same year wrote on the acromegalic constitution. Rolleston states that such an acromegalic state might account for the rare or familial cases of which Lewis analyzed twenty-five examples. Rolleston says that it has been suggested that, in the presence of an acromegaloid state, environmental factors such as an injury might be responsible for the development of frank acromegaly. Such a possibility would be in accord with Engelbach's theory, namely that endocrinopathies may be inherited as a positive or potential endocrinism and that, in the latter, some exciting cause such as infection, trauma, or other exogenic cause may be sufficient to produce a definite endocrinopathy.

Although stating that heredity plays no important rôle in the etiology of acromegaly, Bassoe (1922) states that it has been recorded in a few instances as follows: "Fraenkel, Stedehmann and Benda report a case of typical acromegaly in a man whose brother probably has the same disease, and the father and sister are said to have had similar deforities of the face and extremities. Bonardi reports acromegaly in father and son; Franchin and Gigioli in father and daughter. Schwover and Frantzel each report cases in mother and daughter but only on hearsay evidence in the case of the daughters, and even in themother in Frantzel's report is considered by Marie a case of pulmonary hypertrophic osteoarthropathy and not acromegaly. Machwitz briefly mentions acromegaly in the eighteen year old son of an acromegalic and diabetic father of forty-six. H. Solomon's fourth patient, a mother of fifty-one with typical acromegaly and diabetes, also reported by Schäffer, had a mother who probably suffered from both of these diseases during the last four or five years of her life. Cyon reports the disease in three sisters and Leva in two cousins. Cushing (b) case XXXI, a male acromegalic of large size, had a giant maternal grandfather and his own three children were unusually large at birth. M. T. Croft, a proven case of acromegaly, in his description of his own case, states that the giant Bates was his paternal grand uncle. Goiter and diabetes in relatives are not infrequently mentioned, as is myxedema. Pope and Clark described and pictured an acromegalic father and myxedemic daughter. The patients themselves tall usually come of families made up of people above average size."

Dinkin and Ehrmann (1922) on the basis of forty cases described

acromegaloidism which may, they claim, be of two types, familial or permanent and actual acromegaloidism. The latter is more or less transient, may occur at any time and more nearly than the familial form approach acromegaly.

Possibly the most convincing evidence in favor of the inheritance of gigantism and acromegaly has been presented by Stockard (1931) in dogs. By the process of selective breeding, conditions similar to those found in man, have been produced in dogs. The well proportioned giant, Stockard claims, is illustrated by the Irish wolf hound and the great Dane. In the blood hound, there is pronounced overgrowth of the skin giving excessive long hanging ears, a heavy wrinkling of the forehead and muscles and a dew lap formation; the bones of the extremities are heavy and the entire body has an exaggerated stocky appearance. These symptoms, Stockard claims, are commonly associated with the condition of acromegaly in man. Dogs exhibiting a combination of gigantic form with acromegalic overgrowth are the St. Bernard and mastiff. Many investigators, including Stockard, attribute these conditions in dogs to modifications of the pituitary gland.

Bauer (1937), while admitting that such a condition as gigantism may be inherited, refuses to ascribe its origin to an endocrine dysfunction. He states: "Physicians are inclined to attribute abnormalities in growth to endocrine disturbances, and it is a matter of fact that alteration of thyroid, pituitary or gonadal function may be associated with disorders of growth." "But we must not forget the endocrine hormones

are only one factor among those that influence the height of the body and that in lower organisms, that do not possess any endocrine glands at all such as insects, protozoa or plants, variations in size are obviously dependent upon special primordia which influence the growth directly and act upon cellular activity without any immediate hormonal influence." Bauer, therefore, feels that in the case of gigantism it is not that the individual inherits a special endocrine disturbance that is manifest in abnormal growth, but that the individual inherits a special abnormality in height and that associated with this may be a disturbance of the endocrine glands. Bauer (1924) elsewhere elaborates on this point. He claims that the eunuchoid proportions, frequently found in gigantism, cannot be explained merely because of delayed ossification of the epiphyseal junction of the long bones and hyperactivity of the pituitary or thyroid. He feels that the autochtomous tendency of growth of the bone cells must be considered as an important, individually different factor determining not only definite body length but also body proportions.

Cushing's Pituitary Basophilism: In 1932, Cushing described a syndrome found in fourteen cases that had come to his attention. In the cases that he had an opportunity to examine he found the presence of adenomata of the basophil cells of the anterior lobe of the pituitary. The hyperactivity caused by the presence of adenomata is thought to stimulate the adrenal cortex and other glands to excessive secretion and so cause the series of clinical manifestations described by Cushing in 1932. The involvement of several glands in the syndrome has led some authorities

to regard it as a pluriglandular defect. Cushing's findings, however, led others to feel that the defect is of uniglandular origin and that the term Cushing's basophilism is a more accurate one as it indicates the gland that is the exciting cause of the overactivity of the other glands. Rolleston (1936) states that Cushing's conception has aroused not only great interest but considerable criticism. Meegling and Bates in 1933, he states, suggested that the primary change is in the adrenal cortex and that an associated basophil cell adenoma in the anterior pituitary is secondary. Cushing, on the other hand, believes that a considerable proportion of the cases hitherto attributed to the adrenal actually belongs to what is now known as Cushing's pituitary basophilism.

Cushing (1932) describes the condition as follows: "The disease is characterized by a rapidly acquired plethoric adiposity affecting the face, and neck, and trunk, the extremities being spared. It is associated in women with hypertrichosis and amenorrhea. Other characteristic features are vascular hypertension, purplish striae distensae of the abdomen and acrocyanosis with cutis mammorata of the extremities. It is accompanied by hyperglycaemia and a peculiar softening of the bones of the skeleton has been commonly found at autopsy. In its extreme form the malady has often been encountered in young adults and the average duration of life in fatal cases has been something over five years." Simpson (1937) adds that the disease may also occur in young girls, sexual precocity with menstruation being followed by virilism and amenorrhea. Men, he states, are rarely affected, but, if affected, atrophy of the

testes and impotence as a rule takes place.

No mention of heredity as a factor in the production of Cushing's pituitary basophilism was found in the literature surveyed.

Hypofunction of the Pituitary: Hypofunction of the anterior lobe of the pituitary presents just the opposite somatic manifestations to those produced by hyperfunction. It is defined as an underdevelopment of the entire body and all its organs. Engelbach (1932a--Vol.3) states that it is never associated with pituitary tumor. Rolleston (1936) reports that Biedl has examined several cases of pituitary dwarfism clinically and by X-Ray and that some showed destruction of the sella turica; others gave no evidence of change. There is lack of agreement in regard to the classification of conditions of hypopituitarism and the effects produced by a condition of hyposecretion. Relative to this, Brown (1927) states: "In future a more scientific classification of hypopituitary types will doubtless be possible when the complex metabolic functions of the gland have been sorted out. At the present we can say that lack of growth hormone may so shorten the life cycle that old age comes on before the adult years are reached or merely produce a dwarf. If the sex hormone is also deficient, infantilism of some type results. If the hypothalmic posterior pituitary apparatus is also involved, there will be obesity and perhaps diabetes insipidus. But the permutations and combination of these syndromes seems almost endless."

Pituitary Dwarfism: Pituitary dwarfism is a condition associated with an underfunctioning of the pituitary that is occasionally seen.

Rolleston (1936) states that the condition is rare. Gates (1929) confirms this opinion by saying that ateoleiosis or true dwarfism is rare. Rolleston refers to the condition as pure anterior lobe deficiency or a form of pituitary infantilism. Other authorities, such as Brown (1927), differentiate between dwarfism and infantilism. Engelbach (1932a--Vol.2) defines it as a general arrest of the growth and development of all the organs and systems of the body because of the hypofunction of both the growth and sex principles of the anterior lobe of the pituitary.

Engelbach (1932b) considers that the condition is inherited and not acquired. Rolleston (1936) says that pituitary dwarfism may run in families. Zondek (1935) has described such families. These dwarfs, he claims, also show symptoms of hypothyroidism which can be explained by inadequacy of the thyreotropic hormone. Hereditary dwarfism in mice has been demonstrated by Snell (1929) and by Smith and MacDowell (1930). The work of Snell has already been referred to in this paper. Smith and MacDowell found that the primary causal factor of the dwarfism was an anterior pituitary deficiency and that daily implants of fresh anterior lobe brought the defective mice to normal condition. These investigators found that hereditary dwarfism in mice is associated with the absence of eosinophile cells in the anterior lobe of the pituitary and with deficiencies of other endocrine organs closely resembling those found in hypophysectomized rats. Snell, in publishing his findings with breeding records, concludes that dwarfism behaves in inheritance as a Mendelian character depending on a single gene.

Mayhew and Upp (1932) reported a type of dwarfism for chickens which is similar to the type reported for mice in that it is inherited as a Mendelian recessive. The birds can be distinguished from bantams by certain anatomical differences such as degenerate sex organs. Leonard and Righter (1936) report that Landauer and Aberle state that this dwarfism in fowls is associated with a thyroid deficiency suggesting cretinism. They make no mention of the pituitary glands of the animals. Punnett and Bailey (1914) by studies of crosses between bantams and larger breeds of fowls suggested that the inheritance of weight in poultry involves several factors that are capable of segregating during gametogenesis. Later, Blunn and Gregory (1935) showed that there is an embryological basis of size inheritance from their comparison of the embryos of white leghorns and Rhode Island Reds. The embryos of the heavier breed, the Rhode Island Reds, during the incubation period had more cells per unit volume even though the weights of the embryos of both types were similar. As a result of these experiments, Leonard concludes that there are at least two types of dwarfism in fowl based on a genetical classification. Unfortunately no attempt was made to explain the dwarf condition of the bantam on an endocrine basis even though there is a difference in weight in certain endocrine glands in the different breeds of fowl examined.

Lorain-Levi Dwarfism: There is another type of dwarfism called the Lorain-Levi type in which there is a diminution of all parts of the body with retention of infantile proportions. This is accompanied by genital

underdevelopment and an absence of primary and secondary sex characters. In women menstruation is either not established or is irregular. Brown (1927) states: "It is clear that several different conditions have been described under the label of Lorain type of infantilism. I should be in favor of restricting it to those patients with some evidence of infantilism, who are of normal height, but have an abnormally slender skeleton and sometimes develop alopecia." Hoskins (1933) states that it is due definitely to a failure of the anterior lobe of the pituitary to achieve normal development. In contrast to Brissaud's myxedematous infantilism, the subjects of Lorain type of infantilism are thin and graceful. Mental activity is not retarded.

Rolleston (1936) states that when Lorain infantilism became recognized, it was regarded by Lancereaux in 1893 as idiopathic or anangioplasia (due to general development of the muscular system) or to be degenerative and the result of malnutrition such as may be due to the influence of parental tuberculosis or syphilis. Subsequently it was ascribed in 1901 by Levi to hyperpituitarism.

Engelbach (1932a--Vol.2) considers that heredity is the prime causative factor of the Lorain-Levi syndrome with infection and intoxication playing a secondary exciting role.

Frohlich's Disease: Another clinical disorder which is ascribed to a deficiency of the anterior lobe of the pituitary is what is termed dystrophia adiposa-genitalis or Frohlich's disease. It is characterized by

obesity, genital hyperplasia and faulty skeletal development. Cameron (1935) states that Frohlich's disease can be established in childhood and adult life. He describes the condition as follows: "Juvenile cases exhibit marked adiposity - "juvenile obesity". Most of them are overweight during infancy. When the condition occurs before adolescence various degrees of dwarfism and osseous retardation occur according to the age of onset; infantilism persists." In the cases which occur after the genital and osseous systems have developed, gonadal symptoms may be the only positive pituitary sign accompanying the obesity. Beck (1922) claims that there are many mild cases that do not present a complete clinical picture.

Some authorities feel that Frohlich's disease is caused by tumor. Beck states that a review of earlier literature gives one the impression that the chief etiological factor in this syndrome is either a tumor of the hypophysis or in close proximity to it. Later reports, however, he states, indicate that various other factors are concerned in the etiology and that hypophyseal tumors play a minor role, especially in relation to the incidence of the disease. Engelbach (1932a--Vol.2) holds the same view that he does on other hypopituitary disorders, namely, that tumor is present in only a small proportion of cases. Such a view, Cameron (1935) claims is only valuable in stressing the probably multiple origin of this syndrome.

In discussing the predisposing factors in the etilogy of Frohlich's syndrome, Beck states that there is unquestionably an inherited tendency

in certain families toward the development of endocrinopathies which to some extent follows the Mendelian laws. To quote: "Heredity as a factor has been observed in goitre, myxoedema, cretinism, diabetes, gigantism, and Addison's disease. Because of the analogy between the thyroid and pituitary it is not unreasonable to suppose that the same hereditary tendencies obtain in both glands. Definite data on this point, however, are very meagre." Beck feels that Moebius might have made the same reference to the pituitary that he made to the thyroid when he said that the occurrence of simple goitre, often unnoticed among relatives of patients, is suggestive of congenital alteration of the thyroid; a condition, which can be converted into exophthalmic goitre by the influence of infection. Beck further states that in his own series of cases of dystrophia adiposa-genitalis, the hereditary character was observed in several instances.

Laurence-Moon-Biedl Syndrome: The Laurence-Moon-Biedl syndrome exhibits in addition to the syndrome in Frohlich's disease retinitis pigmentosa, polydactylicism and retarded mentality. Rolleston (1936) states that early cases of this disorder were reported by Horing in 1864, Stor in 1865, and de Wecker in 1866. Others were collected by Cockayne, Krestin, and Sorsby in 1935.

Its familial and congenital nature, Rolleston states, was definitely established by Laurence and Moon in 1866. The mode of inheritance, he says, appears to be autosomal recessive but that it is most improbable that a mutation of a single gene is responsible for the whole syndrome. Rieger and Trauner in 1929 suggested that the epiblastic and mesoblastic

changes are recessive and due to mutation of two genes in the same chromosome. The same conclusion was reached independently by Cockayne in 1933 and by Jenkins and Poucher in 1935. Cockayne, Krestin and Sorsby claim that it has never been recorded in negroes, mongolians, or Indian races. Macklin (1936) has recently analyzed the reported cases of the syndrome with the idea of determining whether the mode of inheritance is through a single recessive gene substitution or through a two gene substitution, one dominant in the autosomes and one a sex-linked recessive. She concluded that the Laurence-Moon-Biedl syndrome may be dependent upon two factors, both of which are necessary before the disease becomes evident, one of which is dominant and autosomal and the other sex-linked recessive.

Bauer (1932), it will be recalled, suggested that in the Laurence-Moon-Biedl syndrome there is a more or less typical combination of several abnormal genes localized in the same chromosomes. He, however, is unwilling to concede that an endocrine disturbance is in any way responsible for its etiology.

Diabetes Insipidus: No attempt was made in the earlier investigations of the pituitary to differentiate between the results due to anterior lobe and posterior lobe deficiency. This was done accidently by the Spanish endocrinologist, Maranon (Hoskins 1933). Maranon had an accident case of a boy who was shot in the forehead. The boy subsequently developed diabetes insipidus, and later died. An autopsy showed the anterior lobe of the pituitary unharmed but the stalk of the pituitary was contracted which presumably prevented the discharge of the posterior

lobe secretion. Hoskins (1933) states that Maranon's case failed as an experiment because the investigator did not rule out injury to the hypothalmus. Hoskins further states that the condition can be produced experimentally be injury to the brain in the neighborhood of the pituitary with or without injury to its posterior lobe. Scientific thought, therefore, is divided as to whether it is fundamentally due to brain injury or pituitary disturbance. That the disease bears some relationship to the pituitary is suggested by Hoskins because the condition, regardless of how it is produced, yields to injections of posterior pituitary extracts. Zonkek (1935) suggests that like all hormonal diseases the syndrome of diabetes insipidus may have various origins. It may originate from the pituitary or be due to cerebral lesions or to peripheral changes.

Baur, Fischer and Lenz (1927) state that diabetes insipidus is also known as hereditary polyuria. They state that a number of genealogical trees have been drawn which show the heredity to be dominant. Mohr (1934) confirms this opinion, saying that the disease is transmitted as a clear cut dominant, and is presumably due to a hereditary dysfunction of the middle part of the pituitary body. Levit and Pessikova (1936) state that the opinion is rather widespread that diabetes insipidus is due to a dominant gene clear cut in its expression. This view, they claim, is based largely upon the well known case of Werk in which the disease was transmitted for six consecutive generations. Similar cases in which the disorder was transmitted for five generations have been reported by Chase and Ganslen and Fritz (Levit and Pessikova (1936).

Levit and Pessikova report that Hogben, on the basis of material gathered by Bulloch, calculated the number of siblings in the respective pedigrees and showed that the ratio of affected to healthy agreed with theoretical expectation, i. e. 1:1 but with a rather high observed number affected.

A study of thirteen cases of diabetes insipidus by Levit and Pessikova showed that three out of the thirteen were familial. As a result of this study, these investigators feel that there is no reason for believing that the disorder is due to a clear cut dominant gene. Furthermore, they feel that it is hardly likely that all the sporadic cases are non-hereditary or even genotypically different from the familial cases. Levit and Pessikova, therefore, concluded that the hypothesis of a conditionally dominant gene showing poor penetrance seems at present plausible. They feel, however, that the genetics of this disease needs further investigation, and report that further work along this line is being carried out at the Maxine Gorky Medico-Genetical Research Institute in Moscow.

Thyroid

Hyperfunction of the Thyroid: Cameron (1935) reports that Plummer believes that there are two distinct entities in hyperthyroidism, exophthalmic goitre or Grave's Disease associated with thyroid hyperplasia and a hyperthyroid state developing from non-hyperplastic goitre. According to Cameron the latter may be termed hyperfunctioning adematous goitre. The hyperfunctioning that occurs in exophthalmic goitre, Cameron states, is considered to be caused by an overactivity of the whole gland,

while that of adematous goitre is caused by a localized reaction in the gland. Engelbach (1932b) states that the etiology of hyperthyroidism is unknown.

Exophthalmic Goitre (Graves' or Basedow's Disease): Exophthalmic goitre is the most important condition, from the point of view of its severity, that is caused by a hyperfunctioning of the thyroid gland. The disease frequently develops suddenly following a fright, mental strain or the like. The individual afflicted is restless and wears an anxious expression. Exophthalmus occurs in fifty per cent of the cases. The metabolic rate is increased, the thyroid is enlarged, the pulse is rapid, and the weight is markedly decreased. Because the disease embodies disturbances of regulatory control and interaction of all organ activities, Graves' Disease appears to be a disease of the nervous system. Some authorities feel that it is caused by an abnormal secretion of the gland rather than simply an increased secretion. Zondek (1935) states that the disease has a very marked predilection for the female sex, the ratio of sex incidence in women and men, according to various writers, being 15:1 to 6:1. Baur, Fischer and Lenz (1931) state that Graves' Disease is eleven times more common in women than in men. In the majority of cases, it does not develop until after puberty although some cases have been observed in children, a few, according to Clifford White (Zondek 1935) in infants.

Baur, Fischer and Lenz (1931) state that not much is known as yet concerning the heredity of Graves' Disease. They state: "There is some

reason to suppose that heredity is dominant, but that for its active manifestation there must cooperate certain contributory external causes." Comprehensive family trees, they feel, might throw more light upon the subject, but that unfortunately they are still lacking. These authors state that Stillman has reported that in the Baltic provinces exophthalmic goitre is found to run in families, but only in the dominant German caste. Siemans in 1917, they state, was able to trace the occurrence of goitre for six generations in a family living in a region where goitre was not endemic. The history of this family showed that the disease seemed to have been dominant; that only the female members of the family were affected, and that the inheritance could be followed in the female line. Baur, Fischer and Lenz further report that in a family described by Agnes Bluhm the inheritance of goitre seemed to have been dominant, but in this family the disorder was transmitted through healthy males as well as females. These investigators state that, because exophthalmic goitre is more prevalent in women than in men, it does not follow that the hereditary predisposition to the disorder is unequally distributed in the two sexes. It may be supposed, they state, that the predisposition becomes active more frequently and more severely in women, just as non-hereditary goitre is much commoner and much larger in women than in men.

Zondek (1935) states that frequently Graves' Disease shows a definite family incidence. The disorder may be transmitted in a like form or in the form of a thyrogenic degenerative constitution.

Howard (1922) speaks of the predisposition that seems to exist in

certain families which he refers to as a thyroid diathesis. In support of his theory, he cites as follows: "Buschari reports a large series of cases with familial tendency. Mackenzie, too, elicited a history of familial predisposition in 44 of his series of 438 cases. Oesterreicher reports a remarkable family: the mother, who was hysterical, had ten children, eight of whom were the subject of exophthalmic goitre, and one of these had three children with the same disease. In Rosenberg's series there was a grandmother, father, two aunts, and two sisters affected. Moss also reports a patient with Graves' Disease whose mother and sister are similarly affected. Thus the disease sometimes affects several members of the same family, or it may occur in successive generations. But what even better still illustrates the "thyroid diatheses" is the occasional incidence of exophthalmic goitre and myxedema in the same family: Thus Arthur Maude reports the case of a myxedematous woman with a son and daughter affected with Graves' Disease and Oppenheimer the case of two sisters, one with myxedema and the other with Graves' Disease." Howard further states that obesity and various neuroses are thought by French clinicians to be more frequently in families of patients with exophthalmic goitre than in normal families. Zondek (1935) notes this also for he says: "In patients' family history neuroses and psychoses are not uncommon."

Cameron (1935) reports that Marine believes, adversely to Worthin and others, that the disease toxic goitre can be acquired especially by women in middle life though cases in early life may be associated with an

inherited or constitutional condition.

Hypofunction of the Thyroid:

Cretinism: Cretinism is a condition found chiefly in children, and it is caused by a congenital absence of the thyroid gland or to an insufficiency of its secretion. Gardiner-Hill (1937) differentiates between endemic and sporadic cretinism on the basis that the pathogenesis of the endemic variety cannot be regarded as one of simple thyroid deficiency. It is described as a condition in which the child is dwarfed both physically and mentally because of thyroid deficiency in foetal life or early infancy. It is characterized by deformity of the head and face; the hair is thin and coarse, the fingers puggy, the abdomen swollen and the sex organs undeveloped. While foetal cretinism is incurable, its victims after birth are markedly improved by thyroid administration. Kimball and Marinus (1930) believe that the mental age of the untreated cretin seldom reaches the age of six years and, if treated, may reach the level of eight years. They feel that this low fixed mental age is the result of maternal hypothyroidism. Emerson (1915) states that cretinism may exist in a mild form, a person in this state showing only one or two symptoms such as rather dry skin or falling out of the hair. Rolleston (1936) speaks of benign hypothyroidism which, he states, is sometimes called non-myxoedematous hypothyroidism. It was described in 1891 as "fruste" or incomplete myxoedema by Thibierge who, in 1897, wrote on thyroid infantilism.

Thyroid Infantilism: Thyroid infantilism, Rolleston (1936) states,

has been defined by Souques and Chauvet in 1913 as a somatic syndrome, characterized by a general arrest of development of the organism by the persistence, in a subject over the age of puberty, of the child morphological features of infancy and hypoplasia of the genitals, absence of the secondary sex characters, dwarfed stature, delayed union of the epiphyses and a child like body. Thyroid infantilism, Rolleston says, is a mild form of cretinism. In 1895 Brissaud described thyroid or myxoedematous infantilism, hence the term Brissaud's type of infantilism is frequently used for the condition. He described an afflicted individual as having a moon like face, fat cheeks, swollen eyelids, and thick lips. Rolleston states that this was then considered the most common form of infantilism but, since then, the pituitary, which also controls the thyroid, is much more often considered responsible.

Adult Myxoedema: Adult myxoedema, another condition due to a hypofunctioning of the thyroid gland, is characterized by a regression of the physical and mental facilities. Gregory (1935) states that the individual becomes dull in mind, sluggish in movement and unsteady in gait. The lack of physical activity, lowered oxidation of foods and excretion of waste result in obesity. Gardiner-Hill (1937) states that there may be an antecedent history of hyperthyroidism, the result of emotional stress or some septic process which has caused an exhaustion atrophy of the gland. Other cases, he claims, result from too great a removal of thyroid tissue at thyroidectomy. Myxoedema may also develop as a result of repeated

pregnancies or it may appear with the termination of ovarian activity at the climacteric. Williamson and Pearse (1930) have suggested that it is the end result of lymphadenoid goitre, in which there may be very little thyroid enlargement but a marked fibrosis of the gland. They, in conjunction with McGarrison, feel that the condition results from a faulty diet, especially deficient in vitamine A rather than iodine (Gardiner-Hill 1937).

Rolleston (1936) states that adult myxoedema has probably not been recognized clinically for as long a time as cretinism because it used to be regarded as oedema, especially that due to renal disease. Means and Lerman in 1935 found that the anemia that may occur early in myxoedema may distract attention from the existence of hypothyroidism. The clinical picture in myxoedema in adults is in many ways similar to that of cretinism in childhood although the onset of the hypothyroidism in the fully developed adult cannot be accompanied by disturbances in growth. Regressive changes in the genital organs are nearly always present.

Non-myxoedematous Hypothyroidism: A condition of hypothyroidism, known as non-myxoedematous hypothyroidism, has recently been recognized. The individual afflicted with this disorder experiences a state of fatigue, loss of strength and lowered metabolism; he is tired and worn out, is nervous and complains of vague pains. Skin and hair changes may be present, and the person may be sensitive to cold. Cameron (1935) states that little advance has been made in recent years in the study of hypothyroidism beyond perhaps the differentiation of this non-myxoedematous state in

adults which is distinct from myxoedema.

Congenital Goitre: Congenital goitre is another condition ascribed to thyroid deficiency. Schiff (1924) states that both maternal goitre and hypothyroidism are considered responsible for congenital goitre.

Engelbach (1932a--Vol.2) states that direct hereditary transmission in the case of thyroidism is now well established. He feels that the thyroid offers a substantial basis for the demonstration of the hereditary etiology of endocrine disorders. To quote: "This gland is definitely related to the early differentiation of the embryonic tissues which are finally developed into the complete systems making up the human body. Abnormal secretion of the thyroid can be traced to a component of the gamete from either parent or as supplied by the mother's thyroid during gravidity. A thyroid insufficiency or excess of thyroxin before fertilization or a decreased or insufficient supply to the embryo is probably the fundamental cause of thyroidism during life. Positive or potential thyroidisms from such a cause are evidenced at birth or are provoked by other exogenous causes affecting the thyroid's function in later life."

Engelbach lists as the endogenous causes of congenital hypothyroidism disorders, age,sex, maturity, reproductive response, heredity and as exogenous causes, infection and intoxication, emotionalism, and trauma. Elaborating on heredity as a causative factor, he states that hypothyroidism at birth or present the first years of life must of necessity be derived from prenatal cause. It is an inherited inactivity of the thyroid gland, he claims, presumably due to a decreased supply of thyroxin to the

foetus which results in a deficient prenatal differentiation and post-natal development and function of the body tissues. While a decreased function of the thyroid gland of the mother during the intra-uterine life of the infant is presupposed to be the paramount etiologic factor, he feels, that the transmission of thyroid deficiency through the male gamete must be included in the causes of congenital hypothyroidism.

Referring to the hereditary and familial occurrence of hypothyroidism, Janney (1922a) says: "The marked hereditary tendency of hypothyroidism, though long recognized, has scarcely been sufficiently emphasized. On account of the sterility frequently accompanying severe hypothyroidism such cases are rarely met. Exceptions do occur such as McIllwaine's cases. More often the parents of cretins show signs of thyroid disease, goitre, thyroitoxicosis, dysthyroidism or mild myxedema. In thyroplasia characterized by congenital absence of the thyroid gland, heredity is to be regarded as the exciting cause of the disease. Both typical cretinism and myxedema have been reported among children of the same family, particularly sisters. C. Herrman described three sporadic cretins and A. G. Paterson two myxedemic patients of the same parents. In the writer's series is an interesting thyroid family showing hereditary obesity, two sisters being myxedemic, a third weighing 225 pounds at fifty years and then developing exophthalmic goitre. Other members suffered from mental diseases. Barrett's remarkable family had 62 members with anomalies ascribable to hypothyroidism. It is probable that with the recognition of increased numbers of light hypothyroid cases with recent new diagnostic aids such as basal

metabolism, the familial tendency will be more often demonstrated. Heredity probably plays an important predisposing as well as exciting etiological role. A study of many cases of hypothyroidism makes it probable that the thyroid tissue of various members of a family may be hereditarily deficient, yet enough being present for all ordinary requirements. However, when undue strain such as many pregnancies, infections, toxemias, etc. occur, sclerotic and atrophic processes ensue in such glands with abnormal rapidity followed by the development of hypothyroidism. Other endocrin glands may be hereditarily deficient in a similar manner."

Baur, Fischer and Lenz (1931) state that Finkbeiner considers that certain "racial factors", that is to say, hereditary factors, contribute to the causation of cretinism.

Cretinoid conditions have been noted in cattle. Cook (1937) reports that genetically controlled defects of the thyroid gland are probably the basis of cretinoid "bulldog" calves which appear in cattle. Craft and Orr (1934) report a case of a cretin calf, a condition similar to the cretinoid condition in children and state that the condition of the glands observed in this case leads them to believe that the abnormalities found in the calf were probably due to a deficiency in the secretion of the thyroid and pituitary. They further state that, although very little is positively known about the influence of the thyroid and pituitary body in cattle, it is probable that these glands are associated with the development of the cattle. Cretins have likewise been reported in Dexter-Kerry cattle by Seligman (1904). Babcock and Clausen (1927) explain the

mode of inheritance of this condition as follows: "The Dexter, the smallest breed of cattle in Great Britain, apparently originated in Ireland, an offshot of the Kerry breed. As compared with Kerry cattle, Dexters are smaller and have shorter legs and broader heads, together with other very characteristic differences. The type is heterozygous as is shown by matings of Dexter and Dexter which give 1 "bulldog": 2 Dextery type: 1 Kerry type (normal): and of Dexter and Kerry which give half Dexter type and half Kerry type offspring." "Bulldog" calves, the authors state, are always still born. They exhibit characteristics that strikingly resemble the cretinoid condition in children. Babcock and Causen[1] say that the simplest explanation of this case is that the Dexter is heterozygous for a factor which produces the "bulldog" calf in the homozygous condition. There is a possibility that the authors refer to the involvement of the thyroid when they say: "A more complex explanation has been offered, but as yet the correctness of it has not been ascertained."

Referring to the etiology of sporadic cretinism, Gardiner-Hill (1937) states that its etiology is intimately associated with endemic goitre and occurs in later generations of families suffering from endemic goitre. He then states: "It is said that heredity is seldom a factor, and this is certainly true in my experience. The picture is typical of simple thyroidism. This may be attributable occasionally to thyroid maldevelopment but usually to atrophic changes in the foetal gland resulting from acute thyroiditis, probably the sequelae of infective disease in the

mother during pregnancy."

Baur, Fischer and Lenz (1931) also note the connection between goitre and cretinism. They state: "Pfaundler, studying 34,500 children found a correlation coefficient of 0.31 ± 0.00 or a correlation index of 0.50 ± 0.00 for the simultaneous occurrence of goitre and cretinism in a particular individual. The correlation between cretinism in the mother appears to be even more marked. In cretinism, too, the notable predominance of maternal influence, the occurrence of the malady in a number of successive members of the same family, and the way in which the condition becomes aggrevated as the generations pass, speak in favor of plasmatic transmission (paraphoria): but hereditary predisposition in the narrower sense of the term must be a contributory cause." Referring specifically to sporadic cretinism, these authorities state that hereditary predisposition is manifestly the decisive factor.

Engelbach (1932a--Vol.3) is apparently undecided as to the etiology of myxoedema, especially in juveniles and young adults. He makes two statements in regard to it. In one place, he states that, in contradiction to other forms of hypothyroidism, with the exception of the goitrous groups, myxoedema in both the juvenile and adolescent ages is due to exogenous causes. Marine fails to agree with Engelbach on this point. He is of the opinion that myxoedema is a terminal state of thyroid exhaustion, consequent to preceding progressive forms of thyroidism. Engelbach contends that support of the theory of the acquired etiology of myxoedema in the child and young adult is its absence during

infancy, its occurrence in healthy juveniles free from signs of previous thyroid disorders and its prevalence following infections. In another place he says that the etiology of myxoedema has not been positively established. Elaborating on this statement, he says that two theories have been advanced to account for the cytologic and consequent biochemical factors referable to its pathogenesis, namely, thyroiditis and iodine deficiency. Another hypothesis is added by Engelbach to the effect that the glandular cytology is due to a combined inherited and exogenic causation.

Janney (1922b) says that congenital goitre is the most frequent hereditary manifestation of the cretinic degeneration, although it is much less frequent than acquired, the ratio being 1:17 for Switzerland according to Demme. In discussing the etiology of the condition, Janney says: "In severely affected Himalayan villages as high as 60% of breast fed children show congenital goiters. On the other hand, cretinism in the offspring is usually preceded by goiter in the parent, 96% of the mothers and 40% of the fathers of cretins had goiter (McGarrison). This writer also ascribed mental shock, worry and depression, also diseases of the mother as etiologically important. With regard to the etiological rôle played by disease, it is well to remember that the lowered resistence of the goitrous individual invites ready attack by bacteria and other toxic agents, so that chronic infection and intoxications are probably to be best regarded in many cases as accompanying phenomenon as well as causative factors in the production of cretinic degeneration in the offspring. Be

this as it may, statistics have definitely established an etiological relationship between goiter in the parents and cretinism in the offspring. Later researches have demonstrated the low iodine content of goiters, therefore, their low hormone content and probable sub-functional condition of such thyroid glands. It would seem, therefore, that the development of congenital goiter may be compensatory as well as possibly due to hereditary lack of normality in the thyroid apparatus of the child." These factors, Janney states, are apparent from Horseby's experiments in which goitrous puppies were born to partly thyroidectomized bitches.

Parathyroids

Comparatively little is known about disturbances of the parathyroids. Rowe (1932) wrote in regard to a discussion of the various endocrine glands: "The parathyroids have been omitted because little is known concerning the disease picture produced by disturbances of their function. On the one hand several different causes may produce a low blood calcium and on the other, the correlation of certain disease states with parathyroid inadequacy rests solely with unchecked speculation."

Hyperfunction of the Parathyroids:

Generalized Osteitis Fibrosa Cystica: One of the most important recent advances associated with the parathyroid glands is the recognition that generalized osteitis fibrosa cystica or von Recklinghausen's disease of the bone is due to a hyperfunctioning of the glands. The association of hyperparathyroidism with the disease was made in 1924. It is caused by edematous change in the parathyroids due to tumor or hyperplasia of the

glands. It is accompanied by a withdrawal of calcium from the bones, causing softening of the bones, deformities of the skeleton and fractures. There is an increased secretion of calcium in the urine. Barney and Mintz (1936) claim that hyperparathyroidism is usually accompanied by the presence of urinary stones, the incidence being practically 70 per cent. The serum calcium is high, serum phosphorus low, and there is increased serum phosphates.

Mandelstamm (1932) states that though much experimental work has been done on the effects of the removal of the parathyroids, very little is known about the results of parathyroid hyperfunction. Reporting on an experiment in which rabbits were injected daily with an extract of horse parathyroids in increasing doses, Mandelstamm states that the most interesting effect noted was a definite protrusion of the eyeball resembling the exophthalmus of Graves' Disease, a result, which he claims, is rarely produced in animals by thyroid administration. Other symptoms were increased appetite, restlessness, and an heightened excitability to galvanic current. Mandelstamm suggests that parathyroid injections produce overaction of the thyroid, thus adding strength to the idea of the interrelationship of the endocrine glands of the body.

Hypofunction of the Parathyroids: Parathyroid insufficiency occurs as post operative tetany following operations upon the thyroid or parathyroids and as spontaneous hypoparathyroidism which Hunter (1937) states is analgous to myxoedema.

Spontaneous or Idiopathic Hypoparathyroidism: Spontaneous or idiopathic hypoparathyroidism is a rare disease. It affects persons

of either sex and at any age. Albright and Ellsworth (1929) describe it as follows: The onset is gradual, the first symptoms being ulnar parathesia, weakness and loss of energy. Later, attacks of tetany supervene and the course of the illness is similar to that of post operative tetany. The serum calcium may be as low as 5 mg. per 1000 cm. and the plasma phosphorous as high as 10 mg. Lenticular opacities may occur and advance to cause blindness.

Engelbach (1932a--Vol. 2) insists that in calcium deficiency of endocrine origin the same general principle as to heredity applies as in other endocrine disorders. An inherent causation, he states, in the nature of a latent or potential hypoparathyroidism is probably present in the majority of cases.

Cheadle in 1877 stated that in the vast majority of cases of laryngism, tetany or general convulsions, a predisposing cause, a special constitutional state of hyperexcitability or mobility or sate or erathism exists and that, because of this, slight causes of irritation set up muscular motor spasms which would not occur in a stable constitution (Engelbach 1932a--Vol. 2).

Relative to the hereditary etiology of tetany, Baur, Fischer and Lenz (1931) say: "Most of the convulsive disorders of infancy (fits and tetany) which the laity are fond of blaming upon teeth are to be regarded as manifestations of the sporadic diatheses; and the same thing is true of laryngismum stridulus. In many families, we find that most of the children perish from one of the convulsive disorders."

They further state that, according to Thiemich and Birk, when children affected with spasmodic diathesis survive into adult life, they usually display anomalies. Kehrer, they state, also showed that tetany of adults, due to a defect in the parathyroids and thyroid, at times runs in families.

Gonads

The rôle of the gonads has been discussed previously in this paper. It was then suggested that there is doubt as to the part that the gonads play as glands of internal secretion during adult life. It is natural, therefore, that authorities should express doubt and different opinions as to the effects produced by alteration of their functional activity in both sexes, particularly in the adult. Rowe (1932) states: "The testicle gives but scant evidence of any endocrine activity in adult years. If there be one, the act of castration will produce a certain hypofunctional state. The evidence again in adult years for a hypergenitalism are wholly wanting. As a single illustration in Barton and Yater's recent admirable compilation - nine common and twenty-nine less frequent causes of priapism are listed, none are associated with an endocrine agent. The chief clinical proponents of the theory of important endocrine activity of the testicle in adult years seem to have adopted the existence of erectile power and the concomitant ability to indulge in intercourse as the principal if not the sole criterion of normal function." Rowe further states that discussion in his book, "Differential Diagnosis of Endocrine

Disorders", is limited to hypofunctional states and even this, he states, involves dubtious assumptions of endocrine activity in the adult human testicle.

Relative to the anomalies of the ovary, Rowe states: "Whatever the character and source of the hormones, the ovary in adult years - at least - is patently an endocrine organ. Removal of these glands - an act producing beyond argument a state of hypofunction, determines certain definite and characteristic changes in a series of purely objective data. An opposite condition connoting an hyperfunction analagous to the clear-cut thyroid and somewhat less certain pituitary relationships has never been, so far as the writer can ascertain, recorded or observed. The establishment of such a diagnosis on the sole basis of a sex urge regarded by the recorder as excessive does not require serious discussion. Ovarian failure is producible and demonstrable; the antithesis has never been recorded on the basis of sound objective evidence."

Hyperfunction of the Gonads: Engelbach (1932a--Vol.2) states that the hypergonadisms in the group of infantile endocrinopathies are comparatively rare and for that reason are comparatively unimportant as compared with the larger group of thyroid and pituitary disturbances. Cameron (1935) says that evidence of hyperactivity of the gonads as a cause of disease remains to be established, although the experiments of Collip and Zondek suggest that chronic hyperactivity may lead to marked pathology. Gregory (1935) differentiates between primary and secondary hypergonadism.

Primary Hypergonadism: Primary hypergonadism includes such conditions as hyperaction of ketolydroxyoestrum which accompanies pregnancy, but which has no unusual effect; the hypersecretion of the corpus luteum which may lead to the inhibition of ovulation; various tumors in children which cause precocious sexual development; and a condition of hyperfunction which may cause an increased sex urge and vicious habits.

Secondary Hypergonadism: The secondary type of hypergonadism is a condition in which gonadal hyperfunction is caused by another gland, the adrenal, producing a syndrome of symptoms. This condition will be discussed under hyperadrenalism.

Hypofunction of the Gonads: Conditions of hypogonadism are apparently more prevalent, or at least more readily recognized than those of hyperactivity, if one can use the amount of literature on the subject as a criterion for judging their relative frequency. Cameron (1935) states that hyposecretion should lead to changes comparable in kind but less in degree than those following castration and occurring at the climacterium. Gregory (1935) classifies the conditions that result from hypoactivity of the gonads as primary non-adipose, primary adipose, secondary hypogonadism and disorders of the menopause.

Primary Non-adipose Hypogonadism: The primary non-adipose type of hypofunction begins at an earlier age than the adipose type. It is characterized by an absence of adiposity. There is an underdevelopment of the musculature and an absence of primary and secondary sex characters. There is a late union of the epiphyses and an overgrowth of the long bones

causing the individual to develop into the long, slender type typical of the eunuchoid. Gastric intestinal and nervous disturbances usually accompany the condition.

Primary Adipose Hypogonadism: The primary adipose type is the result of gonadal deficiency which exhibits a characteristic distribution of adiposity in the mammary mons, and trochanteric regions. This adiposity appears in the individual after the thirtieth year and is due to late castration or a disorder of the gonads. There is an absence of the function of the gonads. Gastro-intestinal disturbances are common. The individual is nervous and usually mentally depressed; is cold and passive, with a loss of libido.

Secondary Gonadism: Secondary gonadism is a gonadal dysfunction due to a hypofunctioning of the glands, especially the pituitary and the thyroid.

Disorders of the Menopause: Disorders of the menopause include disturbances of the menstrual function, leading to amenorrhea, and atrophy of the uterus and vagina.

The etiology of primary adipose eunuchoidism in being a partial inactivity is the same, Engelbach (1932a--Vol.3) states, as the more complete adolescence form. The etiology of the gonadism of the complete castrate is self-evident. Until better explained, Engelbach feels that the incomplete gonadal deficiency, eunuchoidism, should be considered as an inherent defect which is probably transmitted through the gamete.

Bauer (1929) opposes the idea that eunuchoidism is caused by a defect

of an endocrine gland transmitted through the gamete. He maintains that the characteristic height that accompanies eunuchoidism is not due to an abnormality of endocrine function, but is due to an inherent constitutional primordium for overgrowth, an abnormality that may work partially through the endocrine glands, and so produce the accompanying malformation in the genital organs. Bauer states that gigantism associated with hypogenitalism used to be considered as purely the result of insufficient endocrine function of the gonads. He, however, points out that only a limited number of all eunuchoids grow in this way; that the majority do not develop any gigantism at all and that, therefore, the condition must be explained on some other basis.

Certain genital malformations supposedly due to conditions of malfunctioning of the gonads are fairly common, although authorities seem to differ as to whether the gonads or the adrenals are primarily responsible for their presence. Engelbach (1932a--Vol.2) has classified the conditions of agonadism, cryptorchidism and hermaphroditism as conditions of hypergonadism, while Gregory (1935) has classified psuedo-hermaphroditism, and virilism or hirsutism under the heading of adreno-genital syndrome, due to hyperadrenalism. Brown (1927), on the other hand, in his classification of endocrinisms in children, makes no mention of gonadal conditions, but lists as conditions resulting from a hyperfunctioning of the adrenals cortex, sexual precocity and the infant Hercules type, and progeria as an effect of an hypofunctioning of the same gland. Gordon (1936) states that in a study of 519 bodys with cryptorchism, who had been

observed in two endocrine clinics, 398 presented some endocrine disturbance and 121 were negative as far as any endocrine dysfunction was concerned. Gordon found that hypogonadism and cryptorchidism occur almost twice as frequently in the endocrine group as in the non-endocrine in the proportion of 87.5 per cent as against 33.9 per cent. Walker (1937) states that of the male hormone deficiencies with which medical men are called upon to deal with, the commonest are the various deficiencies that are grouped under the headings of eunuchoidism, arrest of normal descent of the testis, and failure in spermatogenesis. In the majority of cases, he states, eunuchoidism is not a pure condition but is associated with deficiencies in other members of the endocrine cycle, especially in the pituitary.

Relative to the causative factor in gonadal malformation, Engelbach (1932a--Vol.2) states that the etiology of the hypogonadal malformations is inherent. Their congenital origin, he feels, is proved by their presence at birth. While admitting that the cases in literature have comparatively little family history which would account for the abnormalities, he, nevertheless, believes that recent developments have shown that embryonic development is undoubtedly influenced to a large extent by endocrine function. Probably maternal endocrinopathies, he states, are present in the histories of many of the cases. He further states that in hypogonadism, related to a suprarenal cortex disorder, direct transmission from parent to child can be demonstrated.

Tanioka (1936), as quoted previously, has demonstrated consecutively

in the case of the pituitary, thyroid, pancreas and suprarenals that acceleration and diminution of the activity of these maternal glands has an effect upon the genital organs of the female foetus. Unfortunately no report is made as to the effect upon the genital organs of the male, and no attempt apparently was made by Tanioka to show that these changes in the genital organs were occasioned by changes in the germ cells which might be passed on to succeeding generations.

The descent of the testes at birth Gordon (1936) claims is due in a large measure to gonadal activators present in the blood of the mother and foetus during pregnancy and in later neonatal life. Cryptorchidism occurs if the testes do not react to the stimulation of the hormone of pregnancy or if the hormone level drops at too early a period before the testes are sufficiently differentiated to respond. The experimental work of Evans, Smith, Engle, Aschheim and others has shown that a gonad stimulating principle is present in the anterior lobe of the pituitary (Engelbach 1932a--Vol.1). Walker (1937) states that other experiments suggest that this principle is two fold: one acting chiefly on the germ cell, and the other on the thecal cells of the ovary and the interstitial cells of the testes.

Baur, Fischer, and Lenz (1931) state that heredity certainly plays a considerable part in the causation of cryptorchidism.

Hermaphroditism is usually divided into two classes, the true and the false. In the true variety not only are there sexual characters of both sexes but also the specific germ cells of both sexes. In the pseudo

form the cells of only one sex are found. Vincent (1925) states that the false variety, which is looked upon as an adrenal defect, is much more common than the true.

Frank (1929) states that approximately eleven individuals are on record in whom the physiological active constituents of both sexes are present, the ovarian portion of the gonad containing ripening follicles and corporea lutea and the testicular portions containing spermatogonia. Jordon (1922), who reviewed the existing literature on hermaphroditism, states that a case described by Sheppard is apparently the most complete case of hermaphroditism recorded for man. Separate testes and ovaries occurred in this case with complete male and female urogenital systems with the exception of the urethra, vagina, and the prostatico cervix of the uterus. In the case which Jordon had the opportunity to observe personally he notes: "In view of the family history of hermaphroditism here considered, its obviously hereditary character, combined with the parsity of data in support of the latter two possibilities, the first possibility may be accepted with considerable confidence."

Baur, Fischer and Lenz (1931) state: "Since in man the development of the sexual characters is determined by the hereditary equipment, we are justified in assuming that the (very rare) cases of true hermaphroditism in human beings develop upon a hereditary foundation." In regard to cases of pseudo-hermaphroditism in which masculine and feminine sexual characters are variously mingled, are beyond question hereditarily determined." They state that Goldschmidt, by combining the hereditary factors

of different races of certain butterflies, has been able to produce intersexual individuals of various kinds. These investigators state that it is not improbable that similar intersexual types can be produced in human beings by a combination of abnormal genes. They further state that numerous cases of pseudo-hermaphroditism are recorded in the Treasury of Human Inheritance, and that inasmuch as a high grade hypospadias is generally to be observed only in one generation of brothers, they are inclined to assume that its heredity is recessive. This, they feel, would be in conformity with the general principle that high grade anomalies are apt to be recessive, and low grade anomalies dominant.

Little apparently is known about the inheritance factor in gonadal dysfunction at the present time. The difficulties involved in a study of the problem are intimately tied up with the general lack of understanding of the relationship of gonadal malfunction and abnormal conditions in man. Relative to this point, Cameron (1935) states that the evaluation of the relationship between endocrine function of the gonads and disease in human beings is less easy than for diseases associated with other endocrine glands, since comparison with animals lower in the scale than primates may lead to error. This is because in the female, the length of cycle and some of the cyclical manifestations are different. Thus in the lower animals all the important events of the cycle, ovulation, mating, greatest growth of the genital organs occur at the height of oestrus, while in the primates, menstruation follows at the end of the period of greatest growth of the secondary organs, but ovulation

occurs usually about midway during the intermenstrum, and mating is not confined to a specific time. Probably, however, the greatest obstacle to satisfactory comparison of reaction to similar stimulus, Cameron adds, is the psyche which holds minimum importance in animals but maximum in man. Clinical evidence is likewise open to some error, Cameron feels, since the subjective symptoms described by the patient are frequently inaccurate. Subjective symptoms, such as interest in the opposite sex and potency, he feels, are particularly open to criticism in considering the possibility of hyperfunction. Rowe's ideas on this point have already been noted. Pratt (1932) holds a similar point of view and considers that conditions such as precocious puberty and increased sex urge can be explained better on other ground than hyperfunction of the testicular endocrine principle.

Adrenals

Lawrence and Rowe (1932) state: "Contrary to the relative frequency with which the pituitary, thyroid and ovarian disorders are encountered, demonstrable adrenal disease seems to be of rare occurrence."

Hyperadrenalism: Authorities offer a variety of opinions as to the effects of hyperadrenalism. Cameron (1935) remarks: "There is excellent evidence through animal experimentation that deficiency of the cortical principle leads to depression of gonad function. But there is no evidence that excess of the principle overstimulates that function." Grollman (1936) substantiates this idea. Swingle and Pfiffner also were unable to

detect any toxic reaction or overdose phenomenon following the administration of large doses of adrenaline to dogs and cats (Cameron 1935). Cameron, however, questions whether the length of time that the experiment was conducted may not have influenced the result.

Hoskins (1933) describes two conditions of hyperfunction of the adrenals. One is a rare disease in which the patient, otherwise apparently normal, is subject to attacks of paroxysmal hypertension. Such cases studied at autopsy have shown tumors of the medulla. The mechanism, Hoskins states, is due to the fact that adrenine is produced in abnormal amounts and episodically is discharged into the circulation.

Adreno-genital Syndrome: The other disorder, due to hyperactivity of the adrenals, and called the adreno-genital syndrome, is a reversion to masculinity associated with carcinoma, adenoma or simple hyperplasia of the adrenal cortex. Spense (1937) states that the cortical changes are more often present without any somatic or sexual disturbance, but, on the other hand, the syndrome may be found when the glands are apparently normal. The clinical manifestations depend on the type of lesion and the time of onset. Malignant tumors, Spense states, are associated with more rapid changes than benign tumors of slow growth or simple hyperplasia. The disease may arise at any age, even developing in utero. Spense states that it is preeminently a disease of the female sex, and affects the male only during childhood. When the overactivity of the glands occurs during foetal life, before sex differentiation has been achieved, the changes in the sex organs are those of pseudo-hermaphroditism. Externally the bodily

configuration approaches the male type. Internally, an uterus and ovaries are present. When the overactivity appears later in foetal life, the external changes are less pronounced, but the uterus and ovaries are atrophic. Goldzeiher (1929) apparently does not hold with Spense, Gregory (1935) and others on the rôle of the adrenals in the production of pseudo-hermaphroditism for he says: "Adrenal hyperplasia in foetal life has been suggested as the cause of pseudo-hermaphroditism, but although it is admitted that such hyperplasia is found at autopsy, the rôle of the adrenal in this condition is still uncertain."

When the disorder occurs after puberty the manifestations are those of precocious puberty. In boys, there is development toward the infant Hercules type. There is precocious growth, and early muscular development, early ossification and dentation, and hair appears early on the pubes, face, and body. In girls, structural growth is increased, and the configuration of the body approaches the male type. The condition, according to Spense, is referred to erroneously as pubertas praecox, for it is in effect a false precocity, since in most cases the patients fail to menstruate. If the condition occurs in adults, it is confined almost entirely to women, and occurs more often between the ages of eighteen and twenty-five. The disorder is accompanied by hirsuties which is characteristic of the male distribution.

Hypofunction of the Adrenals: Relative to the conditions associated with an hypofunctioning of the adrenals, Lawrence and Rowe (1929) say: "The intrinsic association of lowered adrenal activity with the

Addisonian syndrome may be regarded as definitely established. A similar authority does not obtain for that other type of adrenal failure which is assumed to result from a lowered functional activity and to be associated with gross anatomical changes in the gland."

Addison's Disease: The association of Addison's Disease with the suprarenals was established by Addison in 1855. The disease is characterized by anemia, general languor and debility, marked feebleness of the heart's action, irritability of the stomach, and a peculiar change in the color of the skin. Spense states that little has been added to the knowledge of the essential pathology of the disease since Addison described the syndrome. The cortex of the adrenal, and not the medulla, is essential for life, and the fundamental cause of death in this disease is deficiency of the cortical secretion. Spense says that while lack of cortex is responsible for most of the clinical findings it is probable that deficiency of medullary secretion also plays a part in the production of features such as pigmentation, hypotension, and hypoglycaemia. In the majority of cases, the disease is caused by chronic tuberculosis.

The other condition associated with hypofunction of the adrenals, referred to by Lawrence and Rowe, is a syndrome which possesses many of the characteristics of Addison's Disease such as asthenia, hypotension and usually emaciation. The condition, Lawrence and Rowe state, more nearly conforms with the picture of adrenal insufficiency as produced in animal experiments involving interference but not complete extirpation. Spense refers to a third type of failure which is chiefly associated with

suprarenal hemorrhage. It is an acute condition usually terminating fatally in a few days.

The rôle of heredity in the causation of pseudo-hermaphroditism has already been discussed under gonads. Its hereditary character is emphasized by some authorities.

Beck (1922) states that heredity as a factor has been observed in Addison's Disease. His statement is: "Heredity as a factor has been observed in goitre, myxoedema, cretinism, diabetes, gigantism, and Addison's Disease."

Engelbach feels that anomalies of the adrenals, in common with those of other endocrine glands, may be transmitted to the offspring either as a positive or a potential endocrinism.

Grollman (1936) states: "Many predisposing causes have been noted such as worry, emotional shock, alcoholism, heredity, infections - especially malaria, influenza, pneumonia and tuberculosis, but it is doubtful if any except the last named play an etiologic rôle."

Pancreas

Hyperfunction of the Pancreas: Little is known about the conditions of hyperfunction of the pancreas. Gregory (1935) states that a condition of hyperinsulism may exist in the presence of a malignant growth or a benign adenoma of the islet tissue. This condition, when present, produces symptoms of hypoglycaemia, fatigue, irritability, phenomena resembling drunkenness, fear, anxiety, convulsions, and coma. According to

Gregory, there is also a condition of dysfunction of the pancreas in which hyper and hypo conditions alternate.

Hypofunction of the Pancreas:

Diabetes Mellitus: Diabetes mellitus is the well known condition associated with a hypofunction of the islets of Langerhans. This condition is characterized by hyperglycaemia, associated with glycosuria, acetosuria, aceto acetic acid in the urine, and lowered blood base. It is accompanied by thirst, hunger, fatigue, loss of weight, drowsiness, and, in the absence of treatment, by coma and death. There is also a condition of pseudo-hypoinsulism in certain cases of acromegaly that is due to a hyperactivity of the posterior lobe of the pituitary. Cameron (1935) states that some proportion of acromegalics exhibit glycosuria, and that a small proportion exhibit a true diabetes mellitus. He further states that some cases that exhibit concurrent acromegaly and diabetes sometimes recover from the latter spontaneously on or after the removal of a pituitary tumor. Cameron reports that Cammidge believes that a group of cases exists in which hyperactivity of the posterior pituitary causes a persistent glycosuria through too great a degree of neutralization of the effect of insulin. Such cases, if this theory is right, Cameron claims, do not exhibit a true hypoinsulism inasmuch as the normal supply of insulin can be secreted, but is useless. Bergey (1926), as a result of experiments with rabbits, suggests that diabetes mellitus is caused by a filtrable virus. He claims that the disease can be transmitted to rabbits by intravenous administration of a single does of

two cubic centimeters of the urine of a diabetic patient.

The evidence in favor of an inheritance factor in diabetes mellitus is fairly substantial. Pincus and White (1933a) state that the possibility that diabetes mellitus might be inherited has long been entertained by numerous investigators such as Baur, Fischer and Lenz, Cammidge, Finke, Joslin, Kennedy, White and Wright.

Baur, Fischer and Lenz (1931) state that there can be no doubt that in many cases the failure of the cells of the islet tissue is the outcome of a hereditary determined weakness. The fact that diabetes occurs more than twice as frequently in men as in women, they claim, is not indicative of a sex-linked inheritance, but is due to the predominant exposure of males to various external noxious influences which act as the exciting cause of the disease. In conformity with this fact, the authors state that down to the third decade of life the liability of females to diabetes is as great as that of males. Diabetes in youth, they claim, is never due to external causes. These investigators further state that because diabetes is more often hereditarily determined in women than in men, women more frequently inherit a predisposition than do males. They emphasize, however, that this difference is probably not dependent upon a sex-linked inheritance.

Baur reports that Long published three carefully compiled family histories in which an inheritance factor could be traced, and that Buchanan also was able to trace the occurrence of diabetes to heredity in some cases. Buchanan states that in other cases noxious influences,

particularly syphilis and chronic intoxication, were the predominant causative factors. Noorden has published a family tree which seems to indicate that in certain families diabetes has a dominant heredity (Baur, Fischer and Lenz 1931). Hanson is of the opinion that hereditary influences can be shown at work far more often than has been supposed. He believes that the cause is polymeric (Baur, Fischer and Lenz 1931). Baur feels that the reasons for Hanson's deductions are insufficient to justify the exclusion of a far more probable monomeric heredity. He states: "At any rate a simple dominant heredity does not appear to be the rule. If we are seldom able to trace the inheritance of diabetes through several generations, this is presumably because in earlier generations there was often a failure to recognize diabetes, and also, because many carriers of the taint died from some other cause before the outbreak of the disease. Considering the recorded experience as a whole, it seems to me that in most cases diabetes is caused by recessive hereditary factors." The comparative frequency of diabetes in Jews, he feels, also speaks in favor of the notion that the heredity is recessive.

White (1932) suggested that the potentiality for diabetes is inherited as a simple Mendelian recessive. No definite conclusions, White states, were possible because the data in the instance cited were deficient in certain information and no control population was available. All (1933a) reiterated White's suggestion that the potentiality of diabetes may be transmitted as a recessive character. The same year Pincus and White (1933b) after a statistical study of family histories

of 675 diabetic patients, arrived at the conclusion that diabetes mellitus is inherited as a recessive character. These investigators summarize the findings of their study as follows: "The incidences of diabetes are significantly higher in families of diabetic patients than in families of non-diabetic patients. If we accept the assumption that potential diabetics before they develop the disease have the same expectations of life as persons generally, it can be demonstrated that the observed occurrence of diabetes in the children of the diabetic families is in accord with the hypothesis that potentiality for developing diabetes is inherited as a simple Mendelian recessive. The probability that certain parents classed as non-diabetic are genetically diabetic would indicate that there is, on our hypothesis, a deficiency of diabetic children in these diabetic families, but this presumed deficiency may be due to the limitations of the method of collecting family histories. In any event the data behave as if our identification of diabetics among the parents and children were in accord with Mendelian expectations, provided our calculations of the relative number of potential diabetics present in each decade are correct."

Mohr (1934) stated that incomplete dominant cases are also known and suggested that a study of the blood sugar content in the normal members of such families might possibly show a slight increase of the blood sugar which eventually, under unfavorable environmental conditions, might be replaced by real manifest diabetes. Pincus and White (1934) made such a study which showed that approximately 14 per cent of a group

of relatives of diabetics given routine sugar examinations and 25 per cent of those given sugar tolerance tests had abnormally high blood sugar values as compared with similar determinants made upon control groups of normal healthy persons with no family history of diabetes incidence. Commenting on this fact, Pincus and White say: "When we examine, in various types of matings, the incidence of such "hyperglycemic" persons among the offspring, the data suggest that such individuals may be taken as future diabetics, since the ratios in them in these matings are approximately proportional to the ratios of presumed unidentified genetically diabetic individuals called for by the Mendelian hypothesis advanced to explain the inheritance of diabetes." A similar study of the blood sugar of relatives of diabetics was made by Sherril. According to Macklin, Sherril found diabetes in 21 of the 40 supposedly normal relations of 23 of his diabetic patients (Mohr 1934).

Joslin, Dublin and Marks (1937) state that heredity is an important force in the etiology of diabetes, but that its rôle is somewhat obscured by other factors. They state: "These" (referring to factors) "are so interwoven in their operation that it is difficult to isolate the effect of any single one. The situation is, moreover, complicated by the fact that we are concerned in diabetes not so much with the inheritance of the disease as with the inheritance of constitutional abnormalities which predispose the individual to the disease. This predisposition is usually not revealed much before the actual onset of the disease, which is most frequent in middle and later life. We are thus confronted with

the problem of what may be called the "carrier", who may not himself develop diabetes, but who nevertheless transmits the predisposition to his children." In a series of 6357 cases examined, these investigators found that 24.5 per cent of the patients gave a positive family history. Higher percentages were found in special groups such as in women as compared with men; in recent cases as against earlier cases; in diabetic children, especially the living children under observation for an extended period of time, as compared with children who died; in physicians as compared with other patients; in Jewish patients as compared with non-Jewish patients; and in similar as compared with dissimilar twins. They also found that the percentages of diabetic patients with a positive family history of diabetes were higher than those for non-diabetic control groups, and that similar differences were found for siblings of diabetics and non-diabetics. The incidence of diabetes in parents and grandparents of diabetic children was found, they claim, to be from approximately two to two and one-half times the normal. These investigators agree with White that the predisposition to diabetes is probably inherited as a Mendelian recessive character.

From this discussion, it is clear that different investigators have different opinions as to both the mode of inheritance and the relative importance of heredity as an etiological factor in diabetes. White (1937) states that the newer research in the fundamental etiology of diabetes indicates that all cases are hereditary. She claims that the actual proof of the hereditary nature of the disease belongs to

recent years because of the fact that, prior to insulin therapy, the duration of life of the diabetic was so short that the data of family histories were never complete. Joslin (1937) likewise appreciates the importance of the hereditary character of the disease for he says: "The prevention of diabetes depends upon controlling one's heredity."

Other Conditions Associated with Endocrine Dysfunction

Certain conditions, such as hemophilia, hypertension, obesity, mongolianism, and racial differences, have recently been associated with the endocrine glands. While their position in this connection is by no means established, a brief discussion of them seems pertinent.

Hemophilia

Hemophilia is interesting both from the standpoint of heredity and its frequent association with endocrine dysfunction. According to Birch (1932), it is the most hereditary of all hereditary diseases. The transmission is sex-linked, the disease being manifest in males although it is transmitted through the female. Bulloch and Fildes (1911), after reviewing the subject very thoroughly, concluded that there was no adequate proof that the inheritance of hemophilia has ever gone through the male line even through the intermediate step of being carried latent by the daughter of the affected male. Macklin (1928) takes issue with this point of view and points out conditions under which the disease might be transmitted through the male. Mohr (1934) comments on the fact that no conclusive cases of true hemophilia are known in women. Bucura, he states, who has examined critically the known cases of alleged hemophilia in women found that every single case out of the 197 assumed cases had to be excluded. Schloessman observed that quite a few women family members in his large group of cases, who had periods of rather severe bleeding, were heterozygous only. He further observed that the blood of these

heterozygous women had a prolonged clotting time which indicates that the sex-linked gene for hemophilia is not completely recessive (Mohr 1934). Davidson and McQuarry made the same observation in the United States while Weinberg and Thomsen failed to find a similar delay (Mohr 1934). Mohr suggests that possibly other genetic or environment factors may influence the result.

Macklin (1928) states that theoretically it is possible for a woman to show hemophilia as a disease, provided she has a hemophiliac father who had the disease and a mother who was either a carrier or a hemophiliac herself. This may be impossible of realization, Macklin feels, for the presence of a double quantity of the defect may act as a lethal factor inhibiting the development of the embryo.

Mohr states that recently Birch presented evidence to show that ovarian secretion counteracts hemophilia, and that in agreement with this ovarian extracts have a favorable effect against the disease in male bleeders. Mohr feels that if this is the case, the gene for hemophilia, in addition to being sex-linked, is also limited in its effects which means are more pronounced in its effect in one sex or one hormone environment than in the other.

Birch (1932) suggested that the female, in order to transmit the disease, must potentially have the disease, and that there must be something in the female mechanism that holds the disease in abeyance. He points out that the greatest difference between male and female lies in the sex organs, and that the greatest female sex organ is the ovary.

Grant of London in 1904, he states, was the first to bring out this point and to treat successfully a patient with hemophilia with ovarian extract. Later, H. B. Thomas of the University of Illinois College of Medicine treated a hemophiliac patient with fresh ovarian transplant. Birch (1932) reports a study which he has been carrying on for a two year period. The findings are of interest both from the standpoint of the mode of inheritance of hemophilia and the effects of treatment with ovarian extract. He found hemophiliacs have more daughters than sons, while transmittors have more sons than daughters. Over 71 per cent of the transmittors' sons had hemophilia, while only 10 to 15 per cent of transmittors had at least one normal son and no hemophilic sons. Nineteen patients of the 52 studied had received ovarian therapy for more than six months. Nine of these showed a good response; nine showed a definite but less marked change, while one remained unchanged. White (1932) reported three cases of hemophiliacs successfully treated with theelin, two in a family in which three brothers had died of hemorrhage from minor injuries. Cameron (1935) states that more recent reports by Blakie and Hosseck and Bren and Leopold are unfavorable in regard to the efficacy of treating hemophilia with ovarian extract, but Cameron suggests that the administration of larger does might have been more beneficial in these cases.

The fact that hemophilia seems to respond to endocrine treatment has led some investigators to feel that the condition is in some way tied up with an endocrine factor. Smith (1937) holds this idea. Pratt (1932),

referring to the work of Birch, states that even though the results obtained in these small groups are meagre, they are sufficient to stimulate interest and further investigation. The theory of dependence of hemophilia upon gonadal function, he states, is attractive.

Hypertension

The idea that certain cases of hypertension may have a genetical background as well as being associated with an endocrine dysfunction has been suggested by Smith (1937) although he states that it has not yet been proven that hypertension is an endocrine disturbance. Glendenning (1930) states that hypertension has been investigated very intensively to determine its origin. He states: "Physicians are acknowledging the hereditary nature of the condition. Martensen, after a careful review of a large number of cases, concludes that it is definitely hereditary."

Reisman (Davis 1931), in discussing Davis' paper, states in regard to essential hypertension (hypertension in otherwise healthy individuals): "Common as these cases are, the reason why they occur is unknown. Heredity is a factor but not an explanation. Two elements it seems to me are important: psychic and toxic agents. Both of these seem to me to act as vasoconstrictor influences. The psychic factor is ignored by many. The toxic factor has been searched for but so far not with encouraging results. Whether the hypothetic toxins are hormones acting in excess or whether they are disturbances in vitamine metabolism is not known."

Rolleston (1936) states that the hypothesis that excessive secretion of a pressor principle (vaso-pressin or pitressin) by the posterior

lobe of the pituitary may cause essential hypertension corresponds to the view that overproduction of adrenaline has its effect. Rolleston reports that Kraus and Frankie found an increased number of eosinphile cells in the pituitary in cases with high blood pressure. Cushing, he says, argued that the posterior pituitary when infiltrated by basophil cells from the pars intermedia provided a hormone which caused hypertension, while Russell, Evans and Crooker correlated pituitary basophilic adenoma but not basophilic cell invasion of the posterior lobe with a raised blood pressure. Rolleston states that the idea that basophil cell invasion of the posterior lobe is responsible for high blood pressure has been much contested. Spark (1935), as a result of a study of 189 patients, concluded that basophil infiltration does not bear any relation to high blood pressure. Theobald (1934) brought forward evidence against the view that overactivity of the posterior lobe is responsible for arterial hypertension.

Abel, Oliver and Thompson (1937) cite cases in which there was an association of hypertension with hypothyroidism. The Myxedema Committee of London Clinical Society, they state, reported that arteriosclerosis is a frequent accompaniment of long standing myxoedema. Fishberg (1924) reported a case of advanced arteriosclerosis with hypertension and enlargement of the heart in which autopsy showed an extensive atrophy of the thyroid gland. Percy (1912) reported cases of hypertension in which the blood pressure dropped and there was an improvement in renal disease following thyroid medication. Later Duden (1929) reported a case of

myxoedema with hypertension and cardiac enlargement that improved under thyroid medication.

Baur, Fischer and Lenz (1931) refer to constitutional hypertension or hypertonia, which manifests itself as an abnormally high blood pressure, as an hereditary diathesis. The hereditary determination of hypertension, they state, has been mainly elucidated by W. Weitz who sums up the outcome of his investigation as follows: "It seems to me beyond question that a dominant heredity is probable but not certain; and there is a small residue of instances in which production heredity has not been shown to play a part." Baur, Fischer and Lenz state that in Weitz's opinion certain noxious influences, such as alcoholism and nicotinism, formerly thought to play an important part in the production of high blood pressure, are inconsequential. The distribution of hypertension between men and women is about equal. Mon-oval twins are said to resemble each other strikingly in the matter of blood pressure.

Obesity

Newburg and Johnston (1929-1930) state that the physician who prescribes a low caloric diet to reduce the weight of his obese patients frequently deals with subjects who fail to lose weight even on what amounts to starvation diets. These writers have reached the conclusion that such cases are attributable to an abnormality of the endocrine glands, particularly the hypophysis, the thyroid and the gonads. They feel that the logical conclusion to be reached in such cases is that the patients are the victims of a constitutional disease that causes a

progressive disposition of adipose tissue, independent of activity and dietary habits. These authorities state: "Obesity is always caused by an overabundant flow of energy. The excess is deposited as adipose tissue. This disproportion arises from a variety of conditions that may be thought of under two headings. The first group includes the various human weaknesses such as overindulgence and ignorance. The second group is composed of conditions that causes a decrease in the requirement for energy, such as a lessened activity or a lowering of the basal metabolic rate for any reason." Gordon (1937) states that obesity is a manifestation of a general disturbance, and its treatment should be directed against the underlying causes which, he feels, are mainly endocrine.

Baur, Fischer and Lenz (1931) speak of the constitutional tendency of individuals to be obese and state that all varieties of obesity are associated with a disturbance of the internal secretion. In some cases, the disorder is caused by a decline in the functional activity of the thyroid, in others, by defective functioning of the pituitary or to a defective development of the reproductive glands. In still other cases, there seems to be more or less dysfunction of all the glands of internal secretion. These workers report a study made by Weitz and Liebendorfer of 25 cases of obesity during the hunger years of the war. The latter found that there were other cases of obesity in each family. Baur, Fischer and Lenz's conclusions are as follows: "As a rule, the heredity of constitutional obesity appears to be dominant, but in view of the multiformity of the conditions of internal secretion we may presume that

there must be hereditary factors of obesity in which the heredity is of another type."

Goldzieher (1935) urges the use of differential diagnosis of obesity as a means of excluding all exogenous factors. By taking a careful history, he claims, trends are revealed which point to hereditary glandular troubles. If the history reveals a sudden onset of obesity, he feels that a valuable indication of endocrine disorder has been ascertained.

Evans and Strang (1929) have expressed some doubt as to an endocrinogenic factor in obesity and have placed its incidence below one per cent. Grafe and Graham (1911) and Strouse and Dye (1924), on the other hand, feel that the fact that some individuals gain weight while others lose on apparently the same amount of food and exercise, indicates that, even in so-called simple, exogenous obesity, there must be other underlying disturbances, metabolic and endocrine. Eidelsberg (1929-1930) reports a six year study of 151 cases. An analysis of the cases showed the following distribution: 81 were diagnosed as exogenous; 46 as endocrinopathic; 20 as idiopathic or constitutional; 3 as lipontases, lipodystrophy, etc.; and 1 as Decum's Disease. Of the 46 endocrinopathic cases, 28 were pituitary as indicated by girdle obesity, small sella turcica, delayed menses or amenorrhea, deficient sex organs, increased sugar tolerance, etc.; 10 were thyroid in which there was present or absent struma or goitre, low basal metabolism, a slow pulse, myxoedematous infiltration; 2 were thymic origin as indicated by low blood pressure, deficient sex apparatus, positive thymic X-Ray, etc.; 2 were prediabetic as shown by a marked decrease in sugar tolerance; 2 were gonadal,

classified as such because of trochanteric obesity, castration, menopause, etc.; and 2 were of the mixed type or pluriglandular. Eidelsberg reached the following conclusion: "Endogenous obesity is not a myth nor a misconception, while exogenous obesity has often an endogenic or endocrinous etiological factor. Finally, we think, that if we group together all cases of obesity, we will have at one extreme, the purely exogenous obesity, and at the other extreme, the purely endogenous obesity of various types, but between these two extremes the greatest group of mixed cases, all with a metabolic defect, and here and there a so called idiopathic or constitutional case."

Silver and Bauer (1931), on the other hand, give first place to the constitutional group. They state: "While we grant that endocrine dysfunction may be the cause of obesity, we feel that those cases form a small part, numerically almost insignificant part of the obese patients that present themselves in the clinic." "The endocrine system certainly exerts an important influence on the total metabolism. One has only to recall the obesity that usually follows castration, the obesity of Frohlich's syndrome or of adrenal origin to be convinced that endocrine factors can disturb the relationship between energy intake and experditure. That this balance can be shifted in the opposite direction by endocrine dysfunction is illustrated by the cachexia encountered in Graves' Disease, pluriglandular sclerosis and F. Simmond's disease." These authorities feel that it is one thing to be aware that endocrine disorders may cause obesity and quite another to believe that the several

causes of the condition are to be found in the endocrine organs. They place the incidence of obesity due to endocrine origin at approximately 3 per cent. Relative to the rôle of heredity in obesity, Bauer (1929) states that the amount and type of fat distribution over the body is dependent on special primordia that influence the fat tissue itself as well as some endocrine organs and vegetative nervous centers as far as they are connected with the regulation of fat metabolism. He feels that there is little justification for assuming, even in the presence of obesity associated with pituitary changes, that the obese person had inherited an alteration of the pituitary, leading to obesity.

Mongolianism

Mental defectives are classified as idiots, imbeciles, and morons depending upon the degree of mental retardation. Mongolianism is a clinical variety of idiocy associated with the anatomic characteristics of the Mongol.

Various etiologic causes of the condition have been advanced. Syphilis, mental or physical suffering of the mother during pregnancy, advanced age of the mother at the time of conception, reproductive exhaustion due to a large number of pregnancies, and the fact that the father was younger or much older than the mother have been supposed by different authorities to have etiological significance. Macklin (1929), as a result of a survey of the literature on the subject, concludes that there is no adequate support for any of these theories. She presents evidence to show that these and all other environmental influences are

not the cause of Mongolian idiocy, but that it is due to inherited defects and so is germinal in origin. She also feels that there is no support for the view that it is due to the presence of one pair of unit recessive factors. Its mode of inheritance, she feels, appears to be much more complex. She suggests that Mongolian idiocy may be due to the simultaneous presence in the germ cells of five pairs of recessive factors or two dominant and four pairs of recessive factors, carried in as many different chromosomes.

Macklin reports that Brousseau and Brainerd postulate an endocrine dysfunction in the patient himself as the causative factor in Mongolianism. They deny that heredity has a part in its production since in most cases the family history is good. In commenting on this point of view, Macklin states that endocrine disturbances may be the cause, but if so heredity is at the base of the inadequate endocrine system.

Baur, Fischer and Lenz (1931) differentiate between the true Mongolian type and the Mongoloid type. The occurrence of the latter has seldom been noted in several members of the same family. Davenport (1925) records six instances in which only one pair of twins was affected. This strongly suggests, Baur, Fischer and Lenz feel, that special hereditary factors must be at work. Although Siegert records a case in which only one of two monoval twins was Mongoloid, these investigators feel that this does not invalidate the idea of special hereditary factors. Baur, Fischer and Lenz, however, feel that certain influences preceding from the mother are of greater importance than hereditary predisposition.

They are inclined to attribute it to an exhaustion of the hormonal organs of the mother. Davenport suggests a connection with inadequate functioning of the maternal thyroid. While disagreeing with Davenport, Baur, Fischer and Lenz admit that cretinism occurs chiefly in populations containing a strong Mongoloid admixture, e. g. the Alps and other mountainour regions of central Europe.

Schlapp (1925) reports that Crookshank feels that the mongolianism occurring among the white race is an atavism to the orangoid state of development. In support of this interpretation, he makes the assertion that Mongolian idiocy does not occur among true Jews, true Negroes or among the Dravidian population of India. It is confined, he states, to European whites since they constitute the only race more advanced than the Mongol, and hence the only race from which there can be a regression to the Mongolian type. Schlapp disagrees with Crookshank on this point. As a result of twenty years' experience with mongolian feeblemindedness, during which time he investigated and treated about 250 cases, Schlapp found 8 cases of Mongolianism of African descent and 65 per cent of his cases were of Jewish parentage. He disagrees with Crookshank on another point, namely, that the parents or ancestors of Mongolians commonly exhibit more or less marked mongolian characteristics. Schlapp states that in his experience this is almost never the case. Schlapp attributes the condition to an endocrine disturbance. He states: "It is, of course, well known that the Mongolian type of idiot is the child of a mother who is nearing the menopause. At this period of a woman's life the hormone

balance is seriously disturbed. From my own observation and those of many others, it is now safe to conclude that Mongolian idiots are also frequently born of younger women whose endocrines have been disturbed by the drain of infectious diseases and other causes such as emotional strain, exposure to industrialism, etc."

Racial Differences

Some authorities, particularly Keith and Stockard, have attempted to explain racial differences on the basis of endocrine balance. Thus Stockard (1931) states: "It is well known that certain races among men and other mammals tend to be short and small, while others are tall and large; some are stocky and fat while others are thin and lean. We have the race horse type and the draft horse type, the beef cattle and the milk cattle, the dwarf like African pigmy and the tall coastwise Negro, the short statured Japanese and the tall races of China. These racial states are probably related in most cases to genetic tendencies for the determination of a given constitutional balance or, as Sir Arthur Keith has suggested, to a given endocrine complex."

Cognizant of the fact that the growth hormone of the anterior lobe of the pituitary is capable of exercising a profound influence upon the length of the body and of the limbs of the individual and, conversely, that deficiency of this hormone results in individual dwarfism, Hoskins (1933) feels that the supposition is by no means extravagantly far fetched that the Nordic is now tall because of the gradual emergence of

anterior lobe predominance in his ancestral past. Hoskins likewise suggests that it may be possible, if not probable, that the fervent, early maturing, short races may have derived their bodily and mental characteristics, in part at least, from a gradually preponderance of the gonadal hormones. Conversely, he feels, the more phlegmatic, late maturing races may have derived some of their characteristics from relative insufficiency in the secretion of the sex hormone.

Keith, as previously stated, is one of the foremost exponents of the idea that hormonic influence determines racial differences. He believes that the pituitary is the influencing factor in the European, the thyroid in the Mongol, and the adrenal in the Negro. Crookshank, on the other hand, was so impressed with the similarity between the hormonic types or orang and Mongol, chimpanzee and European, gorilla and Negro respectively that he suggested a polygenetic origin for man, each of these races springing from the corresponding anthropoid (Brown 1927). Brown (1927) states that this view presents anthropological difficulties. Keith (1922) accounts for the superficial similarity between certain races and anthropoids, for example, the Mongol and orang, on the basis that they have inherited a common mechanism of growth hormone.

In addition to variations in growth, the endocrine organs are capable of bringing about a change in configuration. Keith, therefore, explains certain racial characteristics on the basis of their relationship to the endocrine organs. Thus he points out that the configuration of a child suffering from marked thyroid deficiency is in many particulars

similar to that of the Mongolian. For example, the growth of the skeleton is in general arrested, but the changes in the head are particularly prominent. The base of the skull fails to develop with the result that the root of the nose seems to be flattened and retracted between the eyes. On the other hand, the upper forehead projects. These are features, Keith points out, that give the Mongol his peculiar facial characteristics. The Negro, to a less degree, shows some of these characteristics. Hoskins (1933) feels that, while the theory that the thyroid is a determining factor in the respects listed, is attractive, it requires considerable ingenuity to fit in all the facts. For instance, he points out that the Mongolian shows to only a slight degree, if at all, a depressed metabolic rate which is one of the accompaniments of thyroid deficiency.

Keith (1922) similarly feels that there may be some connection between adrenal cortex deficiency and skin coloration in the darker races, drawing his conclusions from the fact that in Addison's Disease, a condition produced by adrenal insufficiency, there is a marked darkening of the skin. Hoskins (1933) again points out that adrenal deficiency is characterized by bodily weakness and delayed sexual maturity. Neither is characteristic of the negro. Many of the negro tribes, Hoskins states, are noted for their strength, and, on the whole, the darker races tend to mature earlier than the white race. In evaluating Keith's point of view, Hoskins says: "On the whole the theory that the pattern of evolution has been set by the hormones is not lacking in plausability.

It is, however, by no means adequately supported by specific factual evidence. Whether the anterior pituitary of an adolescent Swede actually produces relatively more growth hormone than does that of a pigmy is not known. Perhaps the nearest approach we have to cogent evidence is the fact recently reported by Riddle that it is possible through selective breeding to produce races of doves characterized by large or small thyroid glands. It is thus shown that nature could have made use of such a working plan whether she did so or not."

Stockard (1931) cautions that, while a thorough analysis of physical race differences is valuable, it should be emphasized that there are frequently extreme type differences within racial groups. There differences, he states, are probably often of genetic origin but they are complicated in other ways. In all cases, they are directly the result of definite growth and developmental reactions. The hereditary type, he states, is transmitted but the expression or development of the type depends upon numerous environmental influences, and although a feature may be definitely inherited it may never be developed or expressed. Elaborating on this point, Stockard states: "We may go still further and claim these types among the British and German are the results more largely of the effects on growth of the environment in which they live rather than of only hereditary differences in the stocks. This position will be borne out if we consider the types in conjunction with other geographical distribution along the coastal plains in maritime climates where there is a rich supply of iodine in the environment

and where the thyroid gland is normally active or hyperactive. The lateral types are largely central continental living in an island environment away from the iodine supply of the sea. The thyroid gland functions poorly in these central continental regions, colloidal goitre is common and in extreme situations cretinism occurs."

Conclusions

As a result of a survey of the literature dealing with the inheritance factor in endocrine dysfunction certain conclusions may be drawn.

The difficulties involved in a study of this sort have already been referred to. The lack of a standard classification of endocrine disorders is significant as it indicates the lack of agreement among authorities. A statement made by Brown, relative to the Lorain-Levi type of infantilism, to the effect that several different conditions have been described under the label of this type of infantilism, might well have been made with reference to other endocrine conditions for a similar situation exists in regard to many of them. One of the chief difficulties, therefore, at the present time is that no clear cut picture prevails in regard to endocrine dysfunctions as is the case in disorders of other systems.

Certain factors may be held accountable for this situation. The comparative recency with which the endocrine glands have engaged the interest and attention of scientists and medical men is a contributing factor. It will be recalled that the presence of an internal secretion was first demonstrated in the case of the testes by Berthold in 1849. Addison in 1855 gave the first adequate description of the constitutional and local effects of the diseases of an endocrine gland, in this case the suprarenals, and it was not until 1894 that the first active principle of an endocrine gland was isolated. The rarity with which

some of the conditions caused by endocrine dysfunction occur is another factor. For example, gigantism is considered a comparatively rare condition, only a relatively few giants ever having been recorded. Cushing in 1932 studied the fourteen cases of pituitary basophilism known to him and other authorities. The number of known cases of human hermaphroditism are reported by various writers to be from four to eleven cases. The interrelationship of the various endocrine glands and the involvement usually of many of them in a given endocrinism is a third factor that complicates the problem. Relative to this point, Brown makes a statement in regard to hypopituitary types which seems equally applicable to other endocrine dysfunctions, namely, that in the future a more scientific classification of hypopituitary types will doubtless be possible when the complex metabolic functions of the gland have been sorted out.

A somewhat similar situation exists in regard to the possible genetic background of endocrinopathies. Authorities differ as to both the possibility and relative importance of heredity in their production. A substantial amount of evidence in favor of an inheritance factor in endocrine dysfunction, as reflected in the statements of various authorities, has been presented. Much of this evidence comes from clinicians, and is based on personal observation and the study of family histories. Baur, Fischer and Lenz state that genealogical trees are valuable in the study of human heredity. Such trees, however, must be carefully and painstakingly compiled and a sufficient number available before conclusions can be profitably drawn. In the material surveyed, it has seemed

that in some instances conclusions have been drawn on meagre evidence, and that what Abraham Myerson terms "the will to find hereditary factors" has been utilized by some endocrinologists. Possibly the most conclusive work that would tend to indicate the hereditary character of an endocrine dysfunction has been done in the case of diabetes mellitus. Here possibly a sufficient amount of material has been analyzed to justify the conclusion that diabetes mellitus is inherited as a Mendelian recessive character.

Considerable confusion apparently exists in regard to hereditary and environmental factors. The problem of differentiating between heredity and environment enters into every problem of genetics. Stockard states that without genetic basis there is no individual and without a suitably arranged complexity of environment the complete genetic basis is unable to produce the normal individual. Whether internal secretions, as factors in the production of conditions ascribed to endocrine dysfunction, are the genetic basis or a part of an unsuitably arranged complexity of environment has not been conclusively shown by most of the authorities investigated.

Scientific evidence that dysfunction of certain endocrine glands is the genetic basis for specific conditions in animals is available. The work of Snell and of Smith and MacDowell has demonstrated that dwarfism due to a dysfunction of the pituitary gland is inherited as a simple recessive character. Genetically controlled defects of the thyroid are probably the basis of cretinoid "bulldog" calves in cattle,

and Stockard has fairly conclusively shown that genetically controlled defects of the pituitary and the thyroid are responsible for many of the modified forms in dogs. Castle states that while there is no direct evidence of this sort of inheritance in man, it is probably similar in man and other mammals.

Many practical difficulties, however, are involved in proving this hypothesis in the case of man. The observation technique is unsatisfactory because of the comparatively equal life span of the investigator and the subject studied. Genealogical studies are useful only under conditions already described. Practical difficulties in laboratory methods, as indicated by Cameron in the case of the gonads, have previously been referred to.

From a survey of the literature on the inheritance factor in endocrine dysfunction it is apparent that there are many gaps in knowledge. The high rate of incidence and disability and incompetence resulting from endocrine disorders, of which a large per cent are apparently preventable or remediable, emphasizes the necessity of further investigation of the problem by both endocrinologists and geneticists.

Bibliography

Abel, Oliver and Thompson, J. W. (1931), Hypertension Associated with Hypothyroidism, Jour. Missouri State Med. Assoc., 28:168-169

Allbright, F. and Ellsworth, R. (1929), Studies on Physiology of Parathyroid Glands, Jour. Clin. Invest., 7:183-201

Allan, William (1933 a), Heredity in Diabetes, Ann. Int. Med., 6;1272-1274

(1933 b), Heredity in Hypertension, Statistical Study, Arch. Int. Med., 52:954-958

Allen, Bennett M. (1921), The Influence of the Thyroid Gland and Hypophysis Upon Growth and Differentiation, Jour. of Heredity, 12:414-422

Aschner, B. (1936), Heredity, Wien. Arch. F. inn. Med., 29:69-94

Babcock, Ernest B. and Clausen, Roy E. (1927), Genetics in Relation to Agriculture, McGraw-Hill, New York

Barney, J. D. and Mintz, E. R. (1936), Relation of Parathyroid Glands to Urinary Lithiasis, Brit. Jour. of Urology, 8:36-44

Bassoe, Peter (1922), Gigantism, in Endocrinology and Metabolism, D. Appleton & Co., New York, 2:807-840

Bauer, Julius (1924), Individual Constitution and Endocrine Glands, Endocrinology, 8:297-322

(1929), Problems of Human Genetics, Bulletin John Hopkins Hospital, 44:52-69

(1932), Constitutional Principles in Clinical Medicine, Harvey Cushing Lectures, 33:37-55

(1936), Relationship between Genetics and Endocrinology, Schweiz. med. Wchnschr., 66:456-460

(1937), Contribution to Problem of Heredity of Endocrine Disorders, Am. Jour. Obst. & Gynec., 33:1077-1080

Bauer, Walter, Allbright, Fuller and Aub, Joseph C. (1929-30), A Case of Osteitis Fibrosa Cystica (Osteomalacia?) with Evidence of Hyperactivity of the Parathyroid Bodies, Metabolic Study II, Jour. Clin. Invest., 8:229-248

Barr, David P. and Bulger, Harold A. (1930), The Clinical Syndrome of Hyperparathyroidism, Am. Jour. of Med. Sci., 179:449-476

Baur, Erwin, Fischer, Eugen and Lenz, Fritz (1931) Human Heredity, George Allen & Unwin L'td., London

Beck, Harvey (1922), Dystrophic Adiposogenitalis, in Endocrinology and Metabolism, D. Appleton & Co., New York, 1:859-924

Behrens, L. H. and Barr, D. P. (1932), Hyperpituitarism Beginning in Infancy: The Alton Giant, Endocrinology, 16:120-128

Bergey, D. H. (1926), Diabetes Mellitus, An Experimental Study on the Etiology of the Disease, Proc. Soc. for Exper. Biol. & Med., 24:229-232

Berman, Louis (1921), The Glands Regulating Personality, The Macmillan Co., New York

Birch, Carroll L. (1932), Hemophilia, Jour. Am. Med. Assoc., 99:1566-1572

Blunn, C. and Gregory, P. (1935), The Embryological Basis of Size Inheritance in the Chicken, Jour. Exp. Zool., 70:397-414

Bonar, B. E. (1935), Endocrine Disease in New Born, Critical Review, Jour. of Ped. 7:99-117

Brown, W. Langdon (1927), The Endocrines in General Medicine, Paul B. Hoeker, Inc. New York

Buchanon, J. Arthur (1923), A Consideration of the Various Laws of Heredity and Their Application to Conditions in Man, Am. Jour. of Med. Sci., 165:675-708

Bullock, William and Fildes, Paul (1911), Hemophilia, Treasury of Human Inheritance, Cambridge University Press, Parts V. & VI:169-354

Cameron, A. T. (1935), Recent Advances in Endocrinology, P. Blaskinson's Sons & Co. Inc., London

Cammidge, P. T. (1928), Diabetes Mellitus and Heredity, Brit. Med Jour. 2:738-741

Castle, W. E. (1938), Personal Correspondence to Author

Cook, Robert (1937), Personnal Correspondence to Author

Craft, W. A. and Orr, H. W. (1924), Thyroid Influence in Cattle, Jour.

of Heredity, 15:255-256

Cunningham, J. T. (1921), Hormones and Heredity, Constable & Co. L'td., London

Cushing, Harvey (1932), Papers Relating to the Pituitary Body, Hypothalmus and Parasympathetic Nervous System, Springfield, Ill.

Danforth, Charles H. (1926), The Interaction of Genes in Development, Proc. Soc. for Exp. Biol. & Med. 24:68-71

(1932), The Interrelationship of Genic and Endocrine Factors in Sex. in Sex and Internal Secretion, The Williams & Wilkins Co., Baltimore, pp 12-54

Davis, N. S. (1931), Hypertension, Jour. Am. Med. Assoc. 97:1295-1299

Dickens, Paul F. and Brown, Omar J. (1937), Present-Day Concepts of Endocrinology, U. S. Naval Med. Bulletin, 35:8-33; 176-195; 387-417

Dinkin, L. and Ehrmann, R. (1922), Acromegaloids, Klin. Wchnschr., I:2139

Duden, Charles (1929), Myxedema with Cardiac Decompensation and Hypertension which Disappeared under Thyroid Medication, Jour. Missouri State Med. Assoc., 26:25-27

Editorial (1924), Dwarfism, Infantilism, Midgets and Lilliputians, Endocrinology, 8:465-466

Eidelsberg, Joseph (1929-30), Obesity, Ann. Int. Med. 3:604-607

Emerson, Charles P. (1915), Essentials of Medicine, J. B. Lippincott Co., Philadelphia

Engelbach, William (1924), Diagnostic Endocrine Clinic, Endocrinology, 8:427-447

(1932)a, Endocrine Medicine, Vol. 1, 2, 3, C. C. Thomas, Springfield, Ill.

(1932 b), Growth Hormone; Report of Case Treated with Evans' Growth Hormone, Endocrinology, 16:1-19

Engelbach, William and McMahon, Alphonse (1924), Osseous Development in Endocrine Disorders, Endocrinology, 8:1-53

Engle, E. T. (1932), Experimentally induced Descent of Testis in Macacus Monkey by Hormones from Anterior Pituitary and Pregnancy Urine;

Rôle of Gonadokinetic Hormones in Pregnancy Blood in Normal Descent of Testes in Man, Endocrinology, 16:513-520

Evans, Frank A. and Strang, James M. (1929), A Departure from the Usual Methods in Treating Obesity, Am. Jour. of Med. Sci., 177:339-348

Fishberg, Arthur M. (1924), Arteriosclerosis in Thyroid Deficiency, Jour. Am. Med. Assoc., 82:463-464

Frank, Robert T. (1929), The Female Sex Hormone, C. C. Thomas, Springfield, Ill.

Fridenberg, Percy (1922), Disorders of Metabolism and Internal Secretion in Relation to the Eye, in Endocrinology and Metabolism, D. Appleton & Co., New York, 2:753-805

Gardiner-Hill, H. (1937), Cretinism and Myxoedema, Brit. Med. Jour., 1:1932-1934

Gates, R. Ruggles (1929), Heredity in Man, The MacMillan Co., New York

Goldzeiher, Max (1929), The Adrenals, The Macmillan Co., New York

(1935), Practical Endocrinology, D. Appleton-Century Co., New York.

Glendenning, Logan (1930), The Human Body, Garden City Publishing Co. Inc., New York

Gordon, Murray B. (1935), The Diagnosis of Endocrine Conditions in Infants and Children, Med. Times & Long Island Med. Jour. 63:376-370

(1936), Endocrine Study of Hypogonadism and Cryptorchidism, New York State Jour. of Med., 36:1313-1318

(1937), Endocrine Obesity in Children, Clinical and Laboratory Studies and Results of Treatment, Jour. of Ped. 10:204-220

Gordon, Murray and Kuskin, Lawrence (1935), Endocrine Studies in Infants and Children, Jour. of Ped. 7:89-98

Gowen, John W. (1937), Contributions of Genetics to Understanding of Animal Disease, Jour. of Heredity, 28:233-240

Grafe, E. and Graham (1911), Über die Anpassungsfähigkeit des Tierischen Organismus an Übereichliche Nahrungszufuhr. Ztsch F. Physical Chem. 73:1-67

Gray, Carolyn E. (1916), Kimber's Anatomy and Physiology for Nurses, The Macmillan Co., New York

Gregory, Jennie (1935), ABC of the Endocrines, The Williams & Wilkins Co., Baltimore

Grollman, Arthur (1936), The Adrenals, The Williams & Wilkins Co., Baltimore

Hammett, Frederick S. (1923), The Thyroid Gland and Development, Jour. of Heredity, 14:294-296

Hannon, R. R., Shorr, E., McClellan, W. S. and Dubois, E. F. (1929-30), A Case of Osteitis Fibrosa Cystica (Osteomalacia?) with Evidence of Hyperactivity of the Parathyroid Bodies, Metabolic Study I, Jour. Clin. Invest. 8:215-227

Hoskins, R. G. (1933), The Tides of Life, W. W. Norton & Co. Inc., New York

Howard, C. P. (1922), Clinical Syndromes Due to Thyroid Disease, in Endocrinology and Metabolism, D. Appleton Co., New York, 1:299-377

Hunter, Donald (1937), The Parathyroid Glands, Brit. Med. Jour., 1:929-932

Huxley, Julian (1922), Ductless Glands and Development, Jour. of Heredity, 13:349-358

Janney, Nelson W. (1922 a), Hypothyroidism, in Endocrinology and Metabolism, D. Appleton Co., New York, 1:379-440

(1922 b), The Cretinic Degeneration, in Endocrinology and Metabolism, D. Appleton Co., New York, 1:441-472

Jennings, H. S. (1924), Heredity and Environment, The Scientific Monthly, 19:225-238

Jordan, H. E. (1922), The Histology of a Fetus from a Case of Human Hermaphroditism with a Consideration of Hermaphroditism in Relation to the Question of Sex Differentiation, Am. Jour. of Ant. 31:27-53

Joslin, E. P. (1928), Treatment of Diabetes Mellitus, 4th. Edition, Lea & Febiger, Philadelphia

(1937), The Prevention of Diabetes and the Prognosis of the Disease, The Commonhealth, 24:137

Joslin, E. P., Dublin, L. I. and Marks, H. H. (1937), Studies in Diabetes

Mellitus: Heredity, Am. Jour. of Med. Sci., 193:8-23

Keith, Sir Arthur (1922), The Evolution of Human Races in the Light of the Hormone Theory, John Hopkins Hospital Bulletin, 33:155-159; 195-201

Kennedy, Samuel (1931), Hereditary Diabetes Mellitus, Jour. Am. Med. Assoc., 96:241-245

Kimball, O. P. and Marinus, C. J. (1930), Relation of Endemic Goiter to Mental Deficiency, Ann. Int. Med. 4:567-577

Kimm, H. T. and Van Allen, A. M. (1932), Hemophilia, Prevention and Treatment of Bleeding with Ovarian Extract, Jour. Am. Med. Assoc., 99:991-993

Lawrence, Charles H. and Rowe, Allan W. (1929), Studies of the Endocrine Glands, V, The Adrenals, Endocrinology, 13:1-39

Leonard, Samuel L. and Righter, James W. (1936), Endocrine Weights of Bantam Fowl, Jour. of Heredity, 27:363-366

Levit, S. G. and Pessikova, L. N. (1936), The Genetics of Diabetes Insipidus, Jour. of Heredity, 27:445-448

Lewis, Aubrey (1934), Acromegaly in One of Uniovular Twins, Jour. Neurol. & Psychopath., London, 15:1-11

Lillie, F. R. (1917), The Free Martin: a Study of the Action of the Sex Hormone in the Foetal Life of Cattle, Jour. Exp. Zool., 23:371-452

Macklin, Madge Thurlow (1928), Heredity in Hemophilia, Am. Jour. of Med. Sci., 175:218-223

(1929), Mongolian Idiocy; Manner of Inheritance, Am. Jour. of Med. Sci., 178:315-337

(1936), The Laurence Moon Biedl Syndrome: Genetic Study, Jour. of Heredity, 27:97-104

Mandelstamm, Maxmilian (1923), Einige Beobachtungen über die Wirkung von Parathyrodin, Ztschr. f. d. Ges. Exper. Med. (Berlin), 35:370-375

(1924), Abstract: Action of Parathyroid Extract, Endocrinology, 8:485

Mayhew, R. and Upp, C. (1932), Inherited Dwarfism in Fowl, Jour. of Heredity, 23:269-276

Means, J. H. and Lerman, J. (1935), Symptomatology of Myxedema: Its Relation to Metabolic Levels, Time Intervals and Ratios of Thyroid, Arch. Int. Med. 55:1-6

Mohr, Otto (1934), Heredity and Disease, W. W. Norton & Co., New York

Newburgh, L. G. and Johnston, Margaret Woodwell (1929-30), Endogenous Obesity - A Misconception, Ann. Int. Med. 3:815-825

New York Times, (1937), Mar., 10:6-5

Park, E. A. and McClure, R. D. (1919), Result of Thymus Extirpation in the Dog with a Review of the Experimental Literature on Thymus Extirpation, Am. Jour. of Dis. Childhood, 18:317-521

Pearl, Raymond (1924), Studies in Human Biology, The Williams & Wilkins Co., Baltimore

Percy, J. F. (1912), Thyroid Extract in Nephritis, Jour. Am. Med. Assoc. 59:1708-1710

Pincus, Gregory and White, Priscilla (1933a), On the Inheritance of Diabetes Mellitus, Am. Jour. of Med. Sci., 186:1-14

(1933b), On Inheritance of Diabetes Mellitus: Further Analysis of Family Histories, Am. Jour. of Med. Sci., 188:159-168

(1934), On Inheritance of Diabetes Mellitus: Blood Sugar Values of Relatives of Diabetics, Am. Jour. of Med. Sci., 188:782-790

Pratt, Jean Paul (1932), Endocrine Disorders in Sex Function in Man, in Sex and Internal Secretion, The Williams & Wilkins Co., Baltimore, pp 880-911

Punnett, R. and Bailey, P. (1914), On Inheritance of Weight in Poultry, Jour. of Genetics, 4:23-39

Randall, L. M. (1936), Disturbances of Genital Physiology Among Women, Texas State Jour. Med., 32:474-482

Reilly, William A. (1935), An Atypical Familial Endocrinopathy in Males with a Syndrome of Other Defects, Endocrinology, 19:639-648

Rolleston, Sir Humphrey (1936), The Endocrine Organs in Health and Disease, Oxford University Press, London

(1937), History of Endocrinology, Brit. Med. Jour., 1:1033-1036

Rowe, A. W. (1932), Differential Diagnosis of Endocrine Disorders, The Williams & Wilkins Co., Baltimore

Rowntree, L. G. (1935), Thymus Gland, Jour. Am. Med. Assoc., 105:592-595

Rowntree, L. G., Clark, J. H. and Hanson, A. M. (1935), Biologic Effects of Thymus Extract (Hanson): Accruing Acceleration in Growth and Development in 5 Successive Generations of Rats under Continuous Treatment with Thymus Extract, Arch. Int. Med. 156:1-29

Rowntree, L. G., Clark, J. H., Steinberg, H. and Hanson, A. M. (1935), Further Studies on the Thymus and Pineal Glands, Ann. Int. Med., 9:359-375

Schaeffer, H. and Denoyelle (1923), Gigantisme Acromegalique Avec Syndrome Adiposo-genital, Rev. Neurol., Paris, 30:346-350

Schiff, E. (1924), The Thyroid Gland, Monatsschr. f. Kinder., 27:359-375

Schloessmann, H. (1935), Heredity, Arch. f. Klin. Chir., 183:371-386

Seligman, C. G. (1904), Congenital Cretinism in Calves, Trans., Path. Soc., London, 4:1-20

Silver, Solomon and Bauer, Julius (1931), Obesity, Constitutional or Endocrine?, Am. Jour. of Med. Sci., 181:769-777

Simpson, S. Levy (1937), Hyperpituitarism, in The Endocrines in Theory and Practice, Blakiston & Son Inc., Philadelphia, pp 25-38

Smith, George V. (1937), Personal Correspondence to Author

Schlapp, Max G. (1923), Causes of Defective Children, Jour. of Heredity, 14:387-391

(1924), Behavior and Gland Disease, Jour. of Heredity, 15:3-17

Smith, P. E. (1927), The Disabilities Caused by Hypophysectomy and Their Repair, Jour. Am. Med. Assoc., 88:158-161

(1930), Hypophysectomy and Replacement Therapy in Rat, Am. Jour. Ant., 45:205-273

Smith, P. E. and MacDowell, E. C. (1930), An Hereditary Anterior Pituitary Deficiency in the Mouse, Ant. Rec., 46:247-257

Snell, G. D. (1929), Dwarf - A Mendelian Recessive Character of the House Mouse, Prod. Nat. Acad. Sci., 15:733-734

Spark, C. (1935), Relation between Basophilic Invasion of Neurohypophysis and Hypertensive Disorders. Arch. Path., 19:473-501

Spense, A. W. (1937), Addison's Disease and Suprarenal Insufficiency, Brit. Med. Jour., 1:275-281

Staff (1929), Collected Publications, No. One, Endocrine Studies, Robert Dawson Memorial, Boston

Stockard, Charles (1931), The Physical Basis of Personality, W. W. Norton Co. Inc., New York

Strouse, Solomon and Dye, M. (1924), Relation Between Food Intake and Body Weight in Some Obese Persons, Arch. Int. Med., 34:267-274

Swingle, W. W. et al. (1933), Function of Adrenal Cortical Hormone and Causes of Death from Adrenal Insufficiency, Science, 77:58-64

Tanioka, T. (1936), The Effect of Functional Disturbance of Maternal Endocrines on Genital Gland of Female Fetus, Jap. Jour. Obst. & Gynec., 19:541-545

Theobald, G. W. (1934), The Alleged Relation of Hyperfunction of the Posterior Lobe of the Hypophysis to Eclampsis and the Nephropathy of Pregnancy, Clin. Sci., London, 1:225-239

Vincent, Swale (1935), Internal Secretion and the Ductless Glands, Physicians and Surgeons Book Co., New York

Walker, Kenneth M. (1937), Hormone Deficiencies in the Male, Brit. Med. Jour., 1:623-624

Watts, Ruth M. (1935), The Effect of Administration of Preparation of Growth Hormone to the Anterior Lobe of the Pituitary upon Gestation and Weight of Newborn Albino Rats, Am. Jour. of Obst. & Gynec., 30:174-185

Werner, August A. (1933), The Effect of the Anterior Lobe Pituitary, the Thyroid and the Gonads upon Preadult Growth, Jour. Missouri State Med. Assoc., 30:398-403

White, C. E. (1932), Treatment of Hemophilia with Theelin, Oklahoma Med. Assoc. Jour., 25:304-305

White, Priscilla (1932), Diabetes in Childhood and Adolescence, Lea & Febiger, Philadelphia

(1937), Inheritance of Diabetes, The Commonhealth 24:135-137

Williamson, G. S. and Pearse, I. H. (1930), Anatomy (Comparative and Embryological) of Special Thyroid Lymph System, Showing Its Relation to Thymus, Brit. Jour. Surg., 17:529-550

Wright, Irving S. (1931), Hereditary and Familial Diabetes, Mellitus, Am. Jour. of Med. Sci., 182:484-497

Zondek, Hermann (1935), The Diseases of the Endocrine Glands, William Wood & Co., Baltimore